Journal of General Chemistry

Vol. 23 No. 3

PHYSICO-CHEMICAL INVESTIGATION OF SYSTEMS CONTAINING HALIDES OF IODINE AND HALIDES OF OTHER ELEMENTS

X. THE SYSTEMS IBr–KBr AND IBr–$AlBr_3$

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In respect of physical and chemical properties the halides of iodine resemble on the one hand free halogens – as had already been noted by D. I. Mendeleev [1] – and on the other hand polar salt-forming halides. • This is true of iodine chloride and iodine bromide.

These iodine halides possess very low polarity in the free state; thus, Luft [3] gives the dipole moment of ICl as 0.5; but in nonpolar solvents (CCl_4 and cyclohexane) it rises to 1.49 and 1.47 [4]. The dipole moment of IBr in bromine solution •• is equal to 1.21 D (L.A. Sheka [5]). In the same paper Sheka showed that the character of the bond in iodine bromide changes with the medium.

Consequently, there are grounds for assuming that ICl and IBr can behave in chemical reactions not only like halogens but also like polar halides. Polarity is developed, for instance, when ICl and IBr react with halides of various elements.

The results of the investigations described in previous communications showed that complex compounds of ICl and IBr with halides of a series of other elements vary in structure in dependence on the polarity and structure of those halides. Thus, the complexes of PCl_5 or PBr_5 with ICl and IBr respectively, possess a structure expressed by the general formula $[PX_4][IX_2]$, where X = Cl or Br [6, 7]. Similar complex anions are characteristic of complexes of the $KX \cdot IX$ type [8, 9, 10].

Whereas iodine is the cation in products of addition of iodine chloride to $SbCl_5$ or $SbCl_3$ ($SbCl_5 \cdot 2ICl$ and $SbCl_5 \cdot 3ICl$ or $SbCl_3 \cdot 5ICl$ and $SbCl_3 \cdot 4ICl$), antimony and chlorine enter into the composition of the complex anion [11]. Analogous conclusions can be arrived at in respect of complex compounds of ICl with aluminum chloride; the structure $I[AlCl_4]$ is attributed to the simplest of these, $ICl \cdot AlCl_3$ by Fialkov and Kaganskaya [8] and by Shor [10].

In view of the results of these investigations, it was a matter of great interest to continue them in the direction of reaction of iodine chloride and iodine bromide both with the highly polar potassium halides and with the nonpolar aluminum chloride and bromide. Among systems of this type the systems ICl-KCl and ICl-$AlCl_3$ have been studied in fair detail [8, 10, 12] in the absence of an organic solvent and in nitrobenzene solutions. The analogous systems IBr-KBr and IBr-$AlBr_3$ have been studied chiefly in nitrobenzene [9], by the methods of electric conductivity measurement, cryoscopy and ion transfer where a great similarity was revealed in the properties of both groups of systems (with chlorides or bromides).

Evidence of formation of complexes in the systems $KX\text{-}IX\text{-}C_6H_5NO_2$ (where X = Cl or Br) is provided by the following facts: a) Potassium halides are insoluble in nitrobenzene but dissolve in it in presence of ICl or IBr; the solutions are good electric conductors, the conductivity of the system $KBr\text{-}IBr\text{-}C_6H_5NO_2$ being of the same order (10^{-3} ohm^{-1}cm^{-1}) as that of the system $KCl\text{-}ICl\text{-}C_6H_5NO_2$ but slightly lower; b) when KCl or KBr dissolves in nitrobenzene solutions of ICl or IBr, the freezing point depression is not only not increased but is even decreased. This signifies that the complexes formed in these systems undergo association; this effect is particularly marked in systems containing bromides.

• The literature on this problem was discussed in the first paper [2].

•• Iodine bromide does not form a compound with bromine.

Ion transfer studies showed that potassium migrates to the cathode, while iodine and chlorine or iodine and bromine – in the form of a complex anion – move to the anode. On the basis of the qualitative characteristics of these processes, the formula $K[IX_2]$ can be attributed to these complexes [9]. Complexes of this composition $KICl_2$ and $KIBr_2$, were obtained in an investigation of the system KCl-ICl by the solubility method [13] and by a preparative method [14].

The electric conductivity of the binary systems KCl-ICl and $AlCl_3$-ICl is somewhat higher than that of these systems dissolved in nitrobenzene when the molar ratio is the same. A definite effect on the electric conductivity of nitrobenzene solutions of these systems is possibly exercised by the association of the resultant complexes.

Data from electric conductivity measurements, cryoscopic examination and study of ion transfer demonstrate the formation of complexes in the systems $IX-AlX_3-C_6H_5NO_2$.

Only one complex, $2ICl \cdot AlCl_3$, is revealed on the melting diagram of the system $ICl-AlCl_3$ [10]. Bearing in mind, however, the instability of this complex and the phenomena observed during a study of the system $ICl-SbCl_3$ [11], it is impossible to exclude the possibility of existence of $ICl \cdot AlCl_3$ in the liquid phase and in nitrobenzene solutions, due to partial dissociation; products of more complicated structure may also be formed due, for example, to further solvation with iodine chloride.

A study of ion transfer, of great interest for the clarification of this problem, showed that the systems $ICl-AlCl_3$ and $ICl-AlCl_3-C_6H_5NO_2$ exhibit some differences in this connection: Migration of iodine to the cathode is observed in the first of these systems, while aluminum and chlorine migrate to the anode [10]; in a nitrobenzene solution of $ICl-AlCl_3$, however, the anolyte was found to have a higher content of aluminum and chlorine as well as of iodine [8]. The influence of the solvent on the process of electrolysis of this and of analogous systems is discussed in the next communication.

For the purpose of elucidation of the composition and nature of the complexes formed by reaction of iodine halides with potassium or aluminum halides, it was also important to compare similar systems containing ICl and chlorides or IBr and bromides of these metals.

Systems of this type, however, containing iodine bromide, have hitherto been inadequately investigated. The electric conductivity of solutions of KBr in liquid IBr has been measured at 45° and 55° [2]. It was of the same order (10^{-2} ohm^{-1}cm^{-1}) as the electric conductivity of the system KCl-ICl (but slightly higher) at the same temperature [10]*, although the electric conductivity of ICl itself at 45° is nearly ten times higher than that of IBr at 45°. The electric conductivity of both systems increases with rising concentration of KCl or KBr.

The electric conductivity isotherms of the systems $IBr-AlBr_3$ [2] and $ICl-AlCl_3$ [10] exhibit the same dependence on concentration with a maximum in the region of approximately 10-12 mole % AlX_3. The first of these systems conducts current more weakly (conductivity at 45° is approximately $10^{-4}-10^{-3}$ ohm^{-1}cm^{-1}) than the second (10^{-3} ohm^{-1}cm^{-1}).

The viscosity of the system $IBr-AlBr_3$ has also been measured at 100° [2]. It was necessary to perform measurements at such a relatively high temperature in order to cover the whole region of concentrations from 0 to 100%**.

The viscosity isotherm has a maximum at a concentration of about 54 mole % $AlBr_3$, very close to the maximum on the molecular electroconductivity curve (at 100°), calculated on IBr as the electrolyte [2]. Consequently, the viscosity measurements at 100° have established the existence of a complex with an equimolar composition.

On the basis of these facts we can assume that at lower temperatures complexes of more complicated composition might be formed. With the aim of confirming this conjecture, it was decided to perform the thermal analysis of the system $IBr-AlBr_3$.

Furthermore, the transfer of ions in the systems $IBr-AlBr_3$ and IBr-KBr was studied with the objective of clarifying the problems discussed above.

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* Due to the relative low solubility of KBr in iodine bromide, measurements could only be performed up to concentrations of approximately 8 mole % KBr.

** See Table 2 for results of thermal analysis of this system.

EXPERIMENTAL

The preparation and purification of the materials and the methods of investigation have been described in the previous communications.

1. System IBr–KBr. Electrolysis and Transfer of Ions.

As was pointed out above, the limited solubility of KBr in fused IBr necessitated the preparation for these experiments of melts containing only 8.4–9.7 mole % KBr. Electrolysis was carried out in a small U-shaped vessel with platinum electrodes in a water thermostat at 40–45°. The current strength was approximately 40 mA. Duration of an experiment 3–4 hours. A dark-grey iodine precipitate was observed to form at the cathode. After the cathode had been washed with anhydrous ether, there remained a crumbly precipitate readily soluble in water to form a solution with a strongly alkaline reaction containing ions of potassium and bromine. A similar phenomenon was observed in the electrolysis of the system ICl–KCl [10].*

Ion transfer experiments were performed in a vessel with platinum electrodes. Current strength 10–12 mA; duration of experiments 22–26 hours at 40–45° (in a water thermostat). At the close of the experiments the liquid from each compartment of the vessel was poured into weighed flasks fitted with ground-glass stoppers.

In order to avoid loss of iodine and bromine during treatment of the electrolyte with a saturated aqueous solution of SO_2 due to the resultant strongly exothermic reaction, the weighed liquids were dissolved in nitrobenzene, after which the SO_2 solution was introduced. The analytical procedure was as for the system ICl–KCl except that the iodine was determined in presence of bromine by a modified Winkler method [15].**

The experimental data for ionic transfer are presented in Table 1 which shows that the potassium content increases in the cathodic section and the bromine content in the anodic section. The iodine content increases in the catholyte but to a relatively small extent.

TABLE 1
Ion Transfer in the System IBr–KBr

No. of Expt.	Comp. of test solution (in mole % KBr)	Amount of copper separated in coulometer (in g)	Substance being determined	Solution after electrolysis				Transfer No		No. of transferred milli-equivalents
				Cathode section		Anode section				
				Required (g)	Found (g)	Required (g)	Found (g)	Catholyte	Anolyte	
1	9.70	0.1842	K	0.2147	0.3111	0.1714	0.0748	0.43	0.43	2.47
			I	6.4720	6.5943	5.1664	5.0419	0.17	0.17	0.96
			Br	4.5154	3.8142	3.6045	4.2997	1.51	1.50	8.69
2	8.41	0.1955	K	0.1911	0.2907	0.1680	0.0683	0.42	0.42	2.55
			I	6.6818	6.8203	5.8735	5.7343	0.18	0.18	1.09
			Br	4.6008	3.8721	4.0414	4.7592	1.48	1.46	8.97

When analyzing these data we must remember that the investigated system IBr–KBr contained a considerable excess of IBr (just as the system ICl–KCl contained a considerable excess of ICl). Electrolysis of the complex formed in the system IBr–KBr is therefore accompanied by electrolysis of iodine bromide. According to the literature [16], during electrolysis of iodine bromide, bromine is deposited at the silver anode and iodine at the cathode.

If we assume that the same complex ($KIBr_2$) is formed in the system IBr–KBr as was obtained from a solution of KBr in fused IBr, then we must conclude that the increase in iodine content of the catholyte substantially represents the difference between the amounts of iodine transferred to the catholyte during electrolysis of IBr and to the anolyte during electrolysis of the $KIBr_2$ complex.

If we also apply the considerations which were expounded in the communication dealing with the system ICl–KCl [10], then we may conclude that in systems of the composition which we have investigated the electrolysis of each mole of $KIBr_2$ is accompanied by electrolysis of approximately 2 moles iodine bromide.

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* An explanation of this phenomenon is given in a previous communication [10].

** The same procedure was followed in the investigation of the system IBr–$AlBr_3$.

2. System IBr–$AlBr_3$. Thermal Analysis.

The same difficulties were encountered in determination of the crystallization temperatures of this system as in the investigation of the system ICl–$AlCl_3$. Visual observations of the crystallization temperatures of solutions of $AlBr_3$ in iodine bromide permitted the determination of temperature arrests only in the concentration region up to 12 mole % $AlBr_3$. Further rise in the $AlBr_3$ concentration resulted in strongly undercooled solutions which at room temperature took the form of a highly mobile liquid; these solutions did not crystallize even when cooled in solid carbon dioxide; in these conditions they formed a viscous, ropy liquid. These phenomena were observed in the concentration range of 12 to 40 mole % $AlBr_3$. Melts containing over 40 mole % $AlBr_3$ crystallized on cooling, but with very small thermal effects which could not easily be detected with the help of a thermometer.

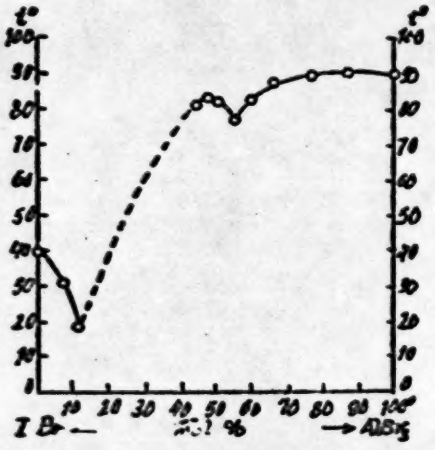
TABLE 2

Thermal Analysis of the System IBr–$AlBr_3$

Mole % $AlBr_3$	Temp. arrests	Mole % $AlBr_3$	Temp. arrests
IBr	40.0°	60.0	83.0
8.0	31.5	66.1	89.0
12.3	18.0	75.6	89.0
44.6	82.0	86.9	90.0
51.7	85.0	100.0	90.0
52.7	83.0		
53.6	82.0		
54.6	78.0		

These difficulties could only be overcome by utilizing the autorecording apparatus of N.S. Kurnakov. With the help of an automatic photorecorder and a simple, differential thermocouple it was possible to establish the melting and crystallization points for the concentration range of 44 to 87 mole % $AlBr_3$. The results of thermal analysis obtained visually and with the photorecorder are presented in Table 2 and in the diagram.

The region of strong undercooling is indicated in the diagram by the broken line; this starts near the first eutectic (about 12 mole % $AlBr_3$, m.p. 18°). The second eutectic (m.p. 78°) contains 54.6 mole % $AlBr_3$, while the dystectic with m.p. 85° corresponds to a content of 51 mole % $AlBr_3$, which confirms the formation of a compound of equimolar composition.



Melting diagram of the system IBr–$AlBr_3$.

Electrolysis and Ion Transfer in the System IBr–$AlBr_3$

Electrolysis of the system IBr–$AlBr_3$ was performed on a solution containing very nearly 30 mole % $AlBr_3$. Experiments were carried out in a small U-shaped cell with platinum electrodes. Duration of experiments 3-6 hours; current strength 14 to 2 mA. For maintenance of the melt in the liquid state the cell was placed in a thermostat at 40-45°. On the surfaces of the cathode were deposited dark-grey crystalline films resembling iodine, the anode was covered with a brown precipitate. Qualitative tests showed that the cathodic deposit consisted of iodine; the anodic deposit, after washing with ether, was found to contain aluminum and bromine. Consequently, the electrolysis of the system IBr–$AlBr_3$ gave results completely analogous with those observed in the electrolysis of the system ICl–$AlCl_3$.

Ion transfer experiments were performed with solutions containing 25-27 mole % $AlBr_3$. Duration of experiments 40-50 hours with a current strength of nearly 2 mA.

Investigation of this sytem met with the same difficulties as in the system ICl–$AlCl_3$: fairly high melting point (around 85°) of the system IBr–$AlBr_3$ at concentrations close to the equivalent composition, high viscosity of the undercooled solutions, excess of iodine bromide in solution, low stability of the IBr · $AlBr_3$ complex, etc. The results of these experiments (Table 3) showed that iodine is transferred to the cathode and aluminum and bromine (in the form of a complex anion) to the anode.

Evaluation of Results. The results of investigation of the systems ICl–KCl and IBr–KBr demonstrate their great similarity, in both of these systems and in nitrobenzene solutions a complex of the same type is formed: $K[IX_2]$ where X = Cl or Br. The above-noted difference between the electric conductivities of these systems is probably due to the differing stabilities of the $KICl_2$ and $KIBr_2$ complexes.

TABLE 3

Ion Transfer in the System $IBr-AlBr_3$

No. of Expt.	Mole % $AlBr_3$	Amount of copper separated in the coulometer (in g)	Substance determined	Solution after electrolysis				Transfer number		Number of transferred milligram-atoms
				Cathodic portion		Anodic portion		Cathodic portion	Anodic portion	
				Calculated (g)	Found (g)	Calculated (g)	Found (g)			
1	25.40	0.0800	Al	0.6192	0.6113	0.3243	0.3321	0.12	0.12	0.29
			I	8.5765	8.7192	4.4924	4.3476	0.45	0.45	1.12
			Br	10.9066	10.6701	5.7129	5.9510	1.17	1.18	2.28
2	37.10	0.0972	Al	0.6839	0.6742	0.6172	0.6270	0.12	0.12	0.36
			I	5.4453	5.5732	4.9167	4.7880	0.33	0.33	1.01
			Br	9.5083	9.2188	8.5800	8.8631	1.18	1.16	3.54

The fact that the order of magnitude of electric conductivity of a nitrobenzene solution of ICl–KCl is different from that of a nitrobenzene solution of IBr–KBr (the first system has a rather better conductivity) might be accounted for by the $KIBr_2$ complex in nitrobenzene solution being more associated than the $KICl_2$.

An equimolar complex, $IBr \cdot AlBr_3$, appears to exist in the system $IBr-AlBr_3$, judging by the data of thermal analysis and by viscosity measurements, whereas a complex of the composition $2ICl \cdot AlCl_3$ is found in the system $ICl \cdot AlCl_3$ judging by the data of thermal analysis. The difference may be due to the circumstance that iodine chloride in the fused state (and also in some nonaqueous solvents) is associated into dimeric molecules which are apparently in equilibrium with the monomer. The dimer dissociates into ions according to the scheme $I_2Cl_2 \rightleftharpoons I^+ + ICl_2^-$. We may, consequently, represent the reaction of complex formation with iodine chloride in the form: $I[ICl_2] + AlCl_3 \rightleftharpoons I^+[AlCl_3 \cdot ICl_2]^-$.

As already noted, complexes of such a composition may undergo stepwise dissociation: $2IX \cdot AlX_3 \rightleftharpoons IX \cdot AlC_3 + IX$. Independently of this difference in composition, the complexes identified by physicochemical analysis of the systems $ICl-AlCl_3$ and $IBr-AlBr_3$ are identical in electrochemical behavior, as shown by measurements of electric conductivity, by electrolysis and by ion transfer data: the cation of these complexes is iodine, while aluminum and chlorine (or bromine) enter into the composition of the complex anion.

SUMMARY

1. The processes of electrolysis and ion transfer in the systems IBr–KBr and $IBr-AlBr_3$ have been studied. It is shown that in respect of the character of the complexes formed in these systems, the latter are very similar to the analogous systems comprising iodine chloride and potassium and aluminium chlorides.

2. A complex of equimolar composition was identified in the system $IBr-AlBr_3$ by the method of thermal analysis.

3. The properties of the systems ICl–KCl and IBr–KBr, $ICl-AlCl_3$ and $IBr-AlBr_3$ are compared.

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Received July 9, 1952

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THE STRUCTURES AND NATURE OF THE COMPLEX COMPOUNDS FORMED BY REACTION OF IODINE HALIDES WITH POTASSIUM OR ALUMINUM HALIDES•

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In previous communications devoted to the physicochemical study of the systems $IX-KX$ and $IX-AlX_3$ (X = Cl or Br) and of the same systems in nitrobenzene solutions [1-6], experimental data were put forward which demonstrated the formation of complex compounds of the type of $KX \cdot IX$, $AlX_3 \cdot IX$ and $AlX_3 \cdot 2IX$. In the same researches Ya. A. Fialkov, K. Ya. Kaganskaya and O.I. Shor discussed the nature and structure of complex compounds of this type.

In the present communication we give more detailed consideration to this problem, mainly on the basis of results of a study of electrolysis and ion transfer.

As a preliminary we must generalize on certain experimental data bearing on the electrochemical properties of the systems in question and of the complex compounds formed.

a) We must point out in the first place that compounds formed in systems consisting of iodine halides and potassium or aluminium halides are fairly good electrolytes: the specific electric conductivity of these systems is of the order of 10^{-3} to 10^{-2} $ohm^{-1}cm^{-1}$.

b) As was shown by a study of nitrobenzene solutions of these systems by the cryoscopic method, complexes of iodine halides with potassium or aluminum halides are capable of association in these solutions.

c) Data for electrolysis• of systems consisting of potassium halides and iodine halides point to the conclusion that the products of electrolysis at the cathode are potassium and a small amount of iodine formed by electrolysis of the excess of iodine halides, while at the anode there is chlorine (or bromine). In the case, however, of electrolysis of nitrobenzene solutions of these systems, potassium accumulates in the catholyte and iodine and chlorine (or bromine) in the anolyte.

d) In the electrolysis of systems containing iodine halides and aluminum halides, iodine goes into the catholyte and aluminum and chlorine (or bromine) into the anolyte in the form of the complex anion. On electrolysis of the nitrobenzene solutions of iodine halides and aluminum halides, however, the anolyte acquires an increased content of aluminum as well as of both halogens.

Comparison and elucidation of the quantitative results on ion transfer in the investigated systems are facilitated by the tables below in which the numbers of ions transferred in each experiment are expressed in g-atoms per g-atom potassium (in systems containing potassium halides) and per g-atom of aluminum (in systems containing aluminum halides) (Tables 1 and 2).

Before proceeding to consider these quantitative data, attention must be drawn to the difficulties associated with a study of these systems by the ion transfer method. Chief among these difficulties is the electrolysis—side by side with the electrolysis of the complex molecules formed in these systems—of the excess of the iodine halides•••; this seriously complicates the interpretation of the quantitative results, since in the chemical analysis of the catholyte and anolyte—after electrolysis—we naturally find only the difference in the amount of iodine or other ions if they are simultaneously transferred to the catholyte and anolyte. Moreover, it was necessary to take into account the side reactions which were observed during the electrolysis of nitrobenzene solutions of the systems $IX-KX$ and $IX-AlX_3$ and the resultant difference in behavior of iodine in systems containing a solvent and those not containing one.

• Communication XI in the series on physicochemical investigation of systems containing iodine halides and halides of other elements.

•• Reference is here made also to results of a study of ion transfer in these and the following systems.

••• For investigation of the binary systems it was necessary to use exess of iodine chloride or iodine bromide consequent upon: 1) the relatively low solubility of potassium halides in fused ICl or IBr; 2) the high melting point of the systems $IX-AlX_3$ when the content of $AlCl_3$ or $AlBr_3$ was close to 50 mole % or higher.

TABLE 1

Relative Numbers of Ions (in g-atoms) Transferred in Experiments with the Systems Iodine Halides-Potassium Halides

Ions	System ICl–KCl [5]				System IBr–KBr [6]				System IBr–$C_6H_5NO_2$ [4]			
	Experiment 1		Experiment 2		Experiment 1		Experiment 2		Experiment 1		Experiment 2	
	Catholyte	Anolyte	Catholyte	Anolyte	Catholyte	Anolyte	Catholyte	Anolyte	Catholyte	Anolyte	Catholyte	Anolyte
K	1	–	1	–	1	–	1	–	1	–	1	–
I	0.6	–	0.8	–	0.4	–	0.4	–	–	1.2	–	1.1
Cl or Br	–	3.3	–	2.8	–	3.5	–	3.5	–	2.2	–	2.1

TABLE 2

Relative Numbers of Ions (in g-atoms) Transferred in Experiments with the Systems Iodine Halides-Aluminum Halides

Ions	System ICl–$AlCl_3$ [5]				System IBr–$AlBr_3$ [6]				System IBr–$AlBr_3$–$C_6H_5NO_2$ [4]							
	Experiment 1		Experiment 2		Experiment 1		Experiment 2		Experiment 1		Experiment 2		Experiment 1		Experiment 2	
	catholyte	anolyte	catholyte	anolyte	catholyte	anolyte	catholyte	anolyte	catholyte	anolyte	catholyte	anolyte	catholyte	anolyte	catholyte	anolyte
Al	–	1	–	1	–	1	–	1	–	1	–	1	–	1	–	1
I	1.4	–	2.6	–	3.9	–	2.8	–	–	5.2	–	8.4	–	6.3	–	6.2
Cl or Br	–	6.6	–	8.2	–	10.3	–	9.7	–	13.3	–	16.4	–	13.3	–	13.2

1. Systems of Iodine Halides-Potassium Halides

Experimental results on ion transfer in systems containing iodine halides and potassium halides (Table 1) permit the following conclusions to be drawn:

a) In iodine halide-potassium halide systems the iodine content increases in the catholyte, although to a relatively slight extent (less than 1 g-atom per g-atom of potassium transferred during the experiment), and correspondingly decreases in the anolyte. In nitrobenzene solution, however, the opposite was the case – the iodine content increased in the anodic portion of the solution.

b) On comparing the number of equivalents (or g-atoms) of chlorine or bromine required for 1 equivalent of potassium, we can infer that in nitrobenzene solutions the composition of the complex compound is evidently simpler because in the solvent-containing system less bromine is required per equivalent of potassium (from 2.1 to 2.2 equivalents) than in a solvent-free system where for each equivalent of potassium transferred to the catholyte we find 3.5 equivalents of bromine transferred to the anolyte. A similar conclusion can be reached by comparing the transfer numbers for potassium and bromine ions as determined from direct analytical data (Table 3).

TABLE 3

Transfer Numbers of Ions in the Systems Potassium Halides-Iodine Halides*

Ions	System ICl–KCl [5]		System IBr–KBr [6]		System IBr–KBr–$C_6H_5NO_2$ [4]	
	Experiment 1	Experiment 2	Experiment 1	Experiment 2	Experiment 1	Experiment 2
K	0.29	0.31	0.43	0.42	0.59	0.51
I	0.19	0.25	0.17	0.18	0.69	0.69
Cl or Br	1.00	0.91	1.50	1.47	1.31	1.04

The fact that in experiments with the systems ICl–KCl and IBr–KBr the chlorine transfer number is close to unity, while for bromine it is even higher than unity, suggests that bromine or chlorine are transferred to the anolyte in the form of a complex ion whose composition in the systems IX–KX is evidently more intricate than in the systems IX–KX–nitrobenzene.

c) The ratio of the amounts of iodine and bromine transferred to the anolyte in one and the same experiment in a nitrobenzene solution of IBr–KBr fluctuates between 1:1.5 and 1:1.8. These data agree in part with those of experiment 3 for the system ICl–KCl-nitrobenzene [3], where the ratio of iodine and chlorine transferred to the anolyte was 1:2.3. On this basis we may suggest that nitrobenzene solutions of the system IX–KX contain a complex anion with

* Tables 3 and 4 present the mean values of transfer numbers calculated on the basis of analyses of the cathodic and anodic liquids.

the composition IX_2^-, i.e. ICl_2^- and IBr_2^-.

The results of our investigation are consequently in full accord with the literature data and indicate that the complexes formed in the systems IX–KX contain potassium as cation (in presence of nitrobenzene it is possibly solvated) and iodine and chlorine or iodine and bromine in the anion.

A more detailed characterization of the investigated systems on the basis of results of a study of ion transfer necessitates knowledge of the ionic mobility or exact values of the transfer numbers. The mobility of the ions present in our investigated systems has not been studied. Greenwood and Emeleus [7] utilized the data of Fialkov and Kaganskaya [3], according to which the transfer number of ICl_2^- in the system ICl–KCl-nitrobenzene can be assumed to be equal to 0.504* (which is very close to the transfer number of Cl^- ions in aqueous solutions). They calculated the mobility of ICl_2^- ions from the magnitude of the mobility of Cl^- in water and from the ratio of the viscosities of water and nitrobenzene. The mobility of potassium ions might also be calculated by this method, but such calculations of ionic mobilities are purely arbitrary.

Concerning the transfer numbers set out in Tables 3 and 4, they fail to give full expression to the structure of the complexes formed in these systems for the following reasons:

a) In the course of ion transfer experiments not only is the complex electrolyzed but also the excess of iodine chloride or bromide present in the investigated systems.

b) The behavior of iodine in the binary systems is different from that in their nitrobenzene solutions; in the latter the iodine liberated at the cathode by discharge of I^+ ions is subsequently transferred to the anolyte due to side reactions [8].

TABLE 4

Ion Transfer Numbers in Systems of Aluminum Halides-Iodine Halides

Ions	System ICl–$AlCl_3$ [5]		System IBr–$AlBr_3$ [6]		System IBr–$AlBr_3$–$C_6H_5NO_2$ [4]			
	Experiment 1	Experiment 2	Experiment 1	Experiment 2	Experiment 1	Experiment 2	Experiment 3	Expt 4
Al	0.13	0.13	0.12	0.12	0.11	0.11	0.10	0.12
I	0.23	0.33	0.45	0.33	0.59	0.87	0.65	0.69
Cl or Br.	1.03	1.08	1.18	1.17	1.48	1.73	1.38	1.60

Nevertheless, on the basis of our experimental data it is possible to establish the composition of the complex and to give an approximate quantitative characterization of the reactions taking place during electrolysis of the investigated systems if we compare the transfer numbers or numbers of equivalents (or g-atoms) of ions which are transferred in the course of the electrolysis. The lack of data for mobility of ions compels us to perform the evaluation on the basis of whether or not the mobilities of the ions in the investigated systems are equal.

As we know the mobilities of K^+, Cl^-, Br^- and I^- ions in aqueous solutions are very similar; it is permissible to assume that they will not differ appreciably also in the systems under investigation. Here we may also remark that Greenwood and Emeleus [7] assume that the mobilities of I^+ and ICl_2^- ions are the same.

Let us apply such considerations to the system ICl–KCl as an example. In order to obtain an approximate idea of the state of this sytem in the course of electrolysis, we must start from the assumption that ion transfer in that system is the result of electrolysis of the complex compound formed in the system and of electrolysis of the excess of iodine chloride; furthermore, we shall assume that the mobilities of the ions in these systems are identical.

If we assume on the basis of preparative studies that the composition of this complex compound is represented by the formula $KICl_4$, then the electrolysis of one mole of such a compound causes one equivalent of potassium to go into the catholyte and one equivalent of iodine and two equivalents of chlorine to go into the anolyte. Let us assume that at the same time electrolysis takes place of $\underline{x}$ moles iodine chloride, so that this would entail the transfer of $\underline{x}$ equivalents of iodine to the catholyte and of $\underline{x}$ equivalents of chlorine to the anolyte.

It follows that in the electrolysis of the system ICl–KCl containing an excess of $\underline{x}$ moles iodine chloride over

* In this work Fialkov and Kaganskaya determined the transfer number only for K^+ ions. It was found to be 0.496, i.e. very close to the transfer number of K^+, in aqueous solutions of KCl (0.498). Greenwood and Emeleus calculated the transfer number of ICl_2^- on the assumption that the complex is represented by the formula $K[ICl_4]$.

the equimolar ratio ICl:KCl, transfer will take place to the catholyte of one equivalent of potassium and of (x−1) equivalents of iodine; at the same time (2 + x) equivalents of chlorine will go to the anolyte.

We are now in a position to calculate the ratios of equivalents of potassium, iodine and chlorine for various values of x.

According to Cornog and Bauer [9], in the system ICl—KCl at temperatures below 45° the formation is possible of an unstable compound KI_2Cl_3 (or KCl · 2ICl). Assuming that a complex of this composition is formed in the KCl—ICl melt, investigated by us, and that the electrolysis of one mole KI_2Cl_3 is accompanied by electrolysis of x moles ICl, we then obtain the following values: transfer takes place to the catholyte of one equivalent of potassium and (x−2) equivalents of iodine, and to the anolyte of (x + 3) equivalents of chlorine.

A comparison of the experimentally found ratios of equivalents of potassium, iodine and chlorine with those calculated as above, confirms that in the system KCl—ICl which we have investigated, the complex $KICl_2$ is subjected to electrolysis. Thus, for example, from the results of the first experiment with the system KCl—ICl (Table 1) the following ratio of equivalents of potassium, iodine (transferred to the catholyte) and chlorine (transferred to the anolyte) is obtained: K:I:Cl = 1:0.6:3.3. These values for iodine and chlorine are higher than those calculated on the assumption that x = 1 (K:I:Cl = 1:0:3) and lower than those on the basis of x = 2 (1:1:4). But if we assume that the mobilities of the ions in the investigated systems are not equal (which is more probable) and that the mobility of the K^+ ion is manifestly greater than that of the ICl_2^- ions, while the mobility of I^+ is lower than that of Cl^-, then a calculation similar to the above one for the system $K^+[ICl_2] + x$ICl gives the ratio K:I:Cl = 1:0:<3 (for x = 1) or 1:<1:<4 (for x = 2).

From the above considerations we may conclude that the electrolysis of 1 mole $KICl_2$ is accompanied by electrolysis of 2 moles iodine chloride, and this would explain the increased transfer of iodine (I^+) to the cathode in comparison with its transfer to the anode in the form of ICl_2^- complex anion. We must remember that in this experiment electrolysis was performed on a solution of 5.5 mole % KCl in fused iodine chloride, i.e., a solution containing a considerable excess of iodine chloride.

This conclusion is confirmed by the results of the second experiment with a melt likewise containing 5.5 mole % KCl.

Thus, the ratios based on the hypothesis that the unstable complex KI_2Cl_3 exists in the KCl—ICl melt are altogether inconsistent with the experimental data. For example, if the hypothesis were correct, there should have been observed a transfer of iodine to the anolyte, whereas in our experiments we observed a transfer of iodine to the catholyte, even though in very small quantity. In the event of formation of KI_2Cl_3, a transfer of iodine to the catholyte would only have been observed after supplementary electrolysis of 3 moles of iodine chloride (x = 3), but in that case 6 equivalents of chlorine would have gone to the anolyte and such a transfer was not observed by us.

Turning now to the quantitative interpretation of the experimental results for ion transfer in the system IBr—KBr, we apply the same calculations as for the system ICl—KCl.

Comparison of the experimentally determined ratios of equivalents of potassium, iodine and bromine with the calculated values permits the conclusion that in the system IBr—KBr the complex $KIBr_2$ undergoes electrolysis.

The ratio of the equivalents of potassium, iodine and bromine, from the data of both experiments (K:I:Br = = 1:0.4:3.5),* is close to the ratios calculated for x = 2 and on condition that the mobilities of ions of K^+ and IBr_2^- (etc.) are not equal (K:I:Br = 1:<1:<4).**

From these data we draw a conclusion similar to that for the system ICl—KCl, namely, that during electrolysis of one mole of $KIBr_2$ electrolysis takes place of 2 moles of iodine bromide.

In the nitrobenzene solution of the system IBr—KBr the ratios of the number of equivalents of ions of potassium and halogens transferred during electrolysis were much simpler (K:I:Br = 1:1.2:2.2 or 1:1.4:2.1) than in the binary systems IX—KX (Table 1). Moreover, in the electrolysis of nitrobenzene solutions of these systems, even when they contained an excess of iodine halide over that corresponding to an equimolar ratio of iodine halide to potassium halide, transfer of both halogens to the anode was observed.

* The concentration in the first case was 8.4 and in the second case 9.7 mole % KBr in IBr melt.

** Reference is to transfer of K^+ and I^+ to the catholyte and of Br_2^- ions to the anolyte (Table 1).

The explanation of the last observation is that the molecular iodine formed at the cathode by discharge of I^+ ions undergoes cathodic reduction ($I_2 + 2\underline{e} \rightarrow 2I^-$) and is transferred to the anode; another possibility is the formation of complexes with the solvent, likewise leading to transformation into I^- ions which go to the anode. Transfer of iodine and chlorine to the anode was observed by Bruner and Galecki [10]. also by Fialkov and Koganskaya [2]; according to the last authors for each $\underline{F}$ there was transferred to the anolyte a little less than one equivalent of iodine and about 1.5 equivalents of chlorine.•

On the basis of the above data we may conclude that the complex $K[IBr_2]$ is present in the nitrobenzene solutions of IBr–KBr that we investigated (molar ratio IBr:KBr = 1:0.22-0.23) and that the electrolysis of one mole of this complex is accompanied by electrolysis of about 0.5 mole of excess iodine bromide.

In conclusion we may say that, making allowance for the complexity of the systems ICl–KCl and IBr–KBr, as well as for the experimental difficulties, the agreement between our experimental and calculated data is sufficiently good and permits us to claim that compounds whose most probable composition is $KICl_2$ and $KIBr_2$ are formed in the systems IX–KX and IX–KX–nitrobenzene.

2. Systems of Iodine Halides-Aluminum Halides

A characteristic feature of the behavior of ions in the systems $IX–AlX_3$ during their electrolysis is transfer of aluminum and chlorine (or bromine) to the anode and of iodine to the cathode (Table 2). From this it follows that iodine is present as cation in the complex compound formed in systems containing iodine halides and aluminum halides, while the anion consists of aluminum and chlorine or aluminum and bromine and is probably solvated by iodine chloride or bromide as evidenced by the large number of g-atoms of chlorine and bromine transferred to the anolyte. The iodine is transferred to the cathodic portion and chlorine (or bromine) to the anodic portion partly as a result of electrolysis of excess iodine halides.

The melting curve of the system $ICl–AlCl_3$ indicates the formation of an unstable compound with the composition $AlCl_3 \cdot 2ICl$ [5]. Taking into account the fact that in ion transfer experiments each g-atom aluminum was accompanied to the anolyte by 7-8 g-atoms of chlorine, we may assume that we are dealing with the complex $I[AlCl_4]$ whose anion is solvated by iodine chloride.

Formation of such solvated complexes is favored by the iodine chloride molecules being associated in the liquid state, in the simplest case as $[I_2Cl_2]$. According to Sandonini and Berghello [11] the latter molecules dissociate into I^+ and ICl_2^-.

Regarding the system $IBr–AlBr_3$, a study of the viscosity [1] and of data for thermal analysis [6] supports the formation of the complex $I[AlBr_4]$.

The results of ion transfer experiments (Table 2) and in particular the high transfer number of bromine (>1) in this system (Table 4), indicate that this complex is likewise susceptible to solvation by iodine bromide.

From the ion transfer data (Tables 2 and 4) the composition of the complex ions in the systems $ICl–AlCl_3$ and $IBr–AlBr_3$ can be established by a procedure similar to that applied for the systems ICl–KCl and IBr–KBr.

Of the possible variants we shall consider the following simplest cases.

1. The complex $I[AlX_4]$ undergoes electrolysis to the accompaniment of electrolysis of $\underline{x}$ moles iodine chloride or bromide. Consequently, $\underline{x} + 1$ g-atoms iodine will go to the catholyte and $\underline{x} + 4$ g-atoms chlorine or bromine•• will go to the anolyte with each g-atom of aluminum.

But since the mobility of $[AlX_4]^-$ ions is evidently lower than the mobility of ions of I^+ and Cl^- (or Br^-), then for each g-atom of aluminum transferred to the anolyte in the form of complex anion, transfer must take place to the catholyte of rather more than $\underline{x} + 1$ g-atoms of iodine, and to the anolyte of slightly more than $\underline{x} + 4$ g-atoms chlorine or bromine.

2. Electrolysis is undergone by the complex $I[AlX_4]$, solvated with $\underline{y}$ moles of IX. At the same time $\underline{x}$ moles of iodine halide (ICl or IBr) are electrolyzed.

If we assume that $\underline{y} = 1$, i.e., that electrolysis is undergone by the complex $I[AlX_4 \cdot IX]$ or $I[X_3AlIX_2]$, content should not change appreciably either in the anolyte or in the catholyte. But if $\underline{y}$ is equal

• It must be remembered that the nitrobenzene solution contain dimeric molecules: $I_2Cl_2 \quad I^+ + ICl_2^-$ [2]

•• In this case it more convenient to base the calculation not on g-equivalents but on g-atoms because the composition of the simplest complex, $I[AlX_4]$, solvated with $\underline{y}$ moles of IX. At the same time $\underline{x}$ moles of iodine halide (ICl or IBr) are electrolyzed

to 2 or more, than not only will the content of aluminum and chlorine in the anolyte increase but also the content of iodine. Each g-atom aluminum requires ($y-1$) g-atoms iodine and ($y+4$) g-atoms chlorine (or bromine).

But if electrolysis simultaneously takes place also of x moles IX, then ($x-y+1$) g-atoms iodine will go to the catholyte, and 1 g-atom aluminum and ($x+y+4$) g-atoms chlorine (or bromine) to the anolyte.

Let us compare the so-calculated values with the experimental ones set out in Table 2 for the system $ICl-AlCl_3$. This comparison shows that the values for the first experiment (Al:I:Cl = 1:1.4:6.6) are very close to those calculated on the assumption that $y = 1$ and $x = 1$ (Al:I:Cl = 1:1:6).* This corresponds to simultaneous electrolysis of the complex $I[AlCl_4 \cdot ICl]$ and 1 mole iodine chloride.

The ratios obtained from the data of experiment 2 (Al:I:Cl = 1:2.6:8.2) are close to those calculated on the assumption that $y = 1$ and $x = 3$ (Al:I:Cl = 1:3:8), which corresponds to the electrolysis of $I[AlCl_4 \cdot ICl]$ and approximately 3 moles iodine chloride. It must be noted that a larger excess of iodine chloride was taken in this experiment than in experiment 1 (in experiment 1 the $AlCl_3$ concentration was 28.8 mole % and in experiment 2 it was 20.6 mole %).

As for the hypothesis that the nonsolvated complex is electrolyzed, the ratios of g-atoms of iodine, aluminum and chlorine transferred in course of electrolysis on this basis are entirely at variance with the experimental data.

Comparison of the experimentally found ratios of amounts of iodine, aluminum and bromine transferred to the catholyte and anolyte during investigation of the system $IBr-AlBr_3$ with the calculated values permits us to draw the conclusion that the complex $I[AlBr_4]$ is solvated by two moles of iodine bromide.

Thus, for instance, the data of experiment 1 for the system $IBr-AlBr_3$ (Al:I:Br = 1:3.9:10.3) are close to the values calculated on the assumption that $y = 2$ and $x = 4$ (Al:I:Br = 1:$\geqslant$3:$\geqslant$10). The results of experiment 2 (Al:I:Br = 1:2.8:9.7) are close to the g-atom ratios when $y = 2$ and $x = 3$. Consequently, electrolysis of the complex $I[AlBr_4 \cdot 2IBr]$ proceeds to the accompaniment of electrolysis of 3-4 moles (depending on the concentration of the starting solution) of iodine bromide. It should be noted that in experiment 1 the concentration of aluminum bromide was 25.4 mole %, while in experiment 2 it was 37.1 mole %.

In attempting a similar characterization of the system $IBr-AlBr_3$—nitrobenzene we come up against even greater difficulties. First, as already noted in the electrolysis of this sytem, the anodic portion receives an increased amount of not only aluminum but also of both halogens. Second, the number of equivalents of bromine transferred to the anolyte reaches quite a high figure.

The fact is that in the system $IBr-AlBr_3$-nitrobenzene the secondary electrolytic processes are more diverse and more complex than in the analogous system containing potassium bromide. The primary transfer of iodine to the catholyte proceeds not only via electrolysis of the excess iodine bromide, but also via electrolysis of the complex $AlBr_3 \cdot nIBr$. The iodine discharged at the cathode subsequently begins to move to the anode.

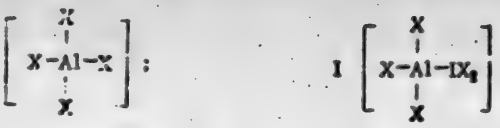
Moreover, this complex is considerably less stable than $KIBr_2$, and in solution it probably exists in equilibrium with its constituents — IBr and $AlBr_3$.

As we know from the literature [12, 13], a solution of aluminum bromide in nitrobenzene is a conductor. The investigations of Sheka and Pecnenaya [14] have established that the cations in such a system are aluminum ions solvated with nitrobenzene. The anions in dilute solutions are predominantly simple bromine ions but in more concentrated solutions the bromine ions exist side by side with complex anions: $AlBr_4^-$, $Al_2Br_7^-$ etc., which are solvated by nitrobenzene.

These simultaneously occurring processes complicate the calculations along the lines of the schemes exemplified above. We are, therefore, compelled to limit ourselves to stating that the complex formed in nitrobenzene solution has the same nature and the same approximate composition as in the solvent-free system, i.e., it consists of $I[AlBr_4]$ solvated with iodine bromide.

The structure of complex compounds of $AlCl_3$ or $AlBr_3$ with iodine halides, of the type of $AlX_3 \cdot nIX$, may be represented by the following schemes:

* On the assumption that the ionic mobilities are not equal and that the mobility of aluminum containing complex anions must be lower than that of halogens, the ratio of the transferred amounts is Al:I:Cl = 1:$\geqslant$1:$\geqslant$6.



etc.

With maintenance of coordination number of 4 for aluminum the molecules of AlX_3 can combine with a maximum of 5 mole[cules] of the halide with formation of the complex $I[Al(IX_2)_4]$.

In a study of the system $SbCl_3$, Ya. A. Fialkov and I.L. Abarbachuk established the existence of the analogous complex compound [illegible] $SbCl_3 \cdot 5ICl$ [15], containing antimony in the complex ion; the cation is iodine. Their structure is evidently the same as that of complex compounds of aluminium halides with iodine halides.

The complex compounds $AlX_3 \cdot nIX$ have low stability and readily undergo dissociation. Rise of temperature accelerates dissociation and leads to cleavage of the iodine halides which had solvated the complex. This is demonstrated by the detection of only a compound with the composition $IBr \cdot AlBr_3$ on the melting curve of the system $IBr-AlBr_3$ at 100° [6], as well as in a study of the viscosity of this sytem [1].

The results of the investigations show that not only highly polar alkali metal halides but also the nonpolar aluminum halides combine with iodine halides to form complexes of the type of binary halides. These complexes are differentiated in structure: The nonpolar aluminum halides combine with iodine chloride or bromide and enter into the composition of complex anions; but the highly polar potassium halides combine with iodine halides in such a manner as to form a complex anion at the expense of their halogen ions, Cl^- and Br^-, and of the iodine halides.

Although compounds of the type of $KCl \cdot ICl$ or $K[ICl_2]$ can be classed as double halides, they are nevertheless closely related to complexes of the polyhalide type and constitute, so to speak, intermediates between the polyhalides—products of addition of molecules of halides to halide anions—and complexes of the double-salt type.

Complex compounds of the type of $I[AlX_4]$ or $I[AlX_4 \cdot nIX]$, also similar compounds of $SbCl_3$ with ICl, are the first representatives of a new series of double halides whose cation is iodine.

SUMMARY

1. An evaluation is made of the results of a study of ion transfer in the systems $IX-KX$ and $IX-AlX_3$ (X being Cl or Br) and of their nitrobenzene solutions.

2. A quantitative characterization is performed of the processes taking place during electrolysis of these systems.

3. Consideration is given to the problem of the composition, structure and nature of the complex compounds formed in these systems in the form of double halides of the general formula $K[IX_2]$ and $I[AlX_4 \cdot nIX]$ or $I[AlY_{4-n}(IX_2)_n]$.

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Received July 9, 1952

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AN IRREVERSIBLE-RECIPROCAL SYSTEM OF THE SINGULAR TYPE WITH LAYER FORMATION FROM THE SULFATES AND CHLORIDES OF LITHIUM AND SILVER

D. S. Lesnykh and A. G. Bergman

Analysis of the ternary reciprocal systems of chlorides and sulfates which have been investigated by us and by other authors shows that all the systems with participation of salts of lithium and salts of alkali metals and alkaline earth metals (separately) belong to the type of systems with unlimited reciprocal solubility of the components in the fused state. But in systems with participation of salts of lithium and thallium, lithium and lead, and lithium and cadmium, there is limited reciprocal solubility in melts of the components of stable pairs. On the other hand, the components of stable pairs of chloride-sulfate systems with participation of salts of silver and thallium [1] and silver and cadmium [2] only have a tendency to form layers, whereas in the system constituted by the salts of silver and sodium [3] the components of the stable pair exhibit limited reciprocal solubility in the fused state.

TABLE 1
Binary Systems (Fig. 1).

Systems	Characteristic points of curve	Data of other authors		Our data	
		%*	M.p.	%	M.p.
$LiCl \rightarrow AgCl$	Continuous series of solid solutions without minimum and maximum	[5]		–	–
	Homeomorphic transformation of LiCl	–	–	–	560
$Ag_2Cl_2 \rightarrow Ag_2SO_4$	Eutectic	47	304 [1]	–	–
	Polymorphic transformation of Ag_2SO_4	–	412	–	–
$Ag_2SO_4 \rightarrow Li_2SO_4$	Congruent compound $3Ag_2SO_4 \cdot 2Li_2SO_4$, giving a continuous series of solid solutions with the components	40	572 [5]	–	–
	Eutectic I	–	–	25	567
	Congruent compound $Ag_2SO_4 \cdot Li_2SO_4$	–	–	50	575
	Eutectic II	–	–	68.5	556
$Li_2Cl_2 \rightarrow Li_2SO_4$	Eutectic	53.5	478 [6]	53	478
	Polymorphic transformation of Li_2SO_4	–	572	–	572
	Homeomorphic transformation of LiCl	–	–	–	564

These facts justify the assumption that layer formation in melts in the majority of cases is due to the presence in the system of ions with a different structure of the outer electron shells (inert-gas type on the one hand, and containing 18 or 18 + 2 electrons on the other hand), possessing a different polarization character and forming salts of a stable pair with sharply divergent physicochemical properties. An exception is provided by the system of chlorides and sulfates of lithium and zinc, whose components exhibit unlimited solubility in the liquid state and tend strongly to form complexes.

For the purpose of confirming the above hypothesis we have studied the ternary reciprocal system of the chlorides and sulfates of lithium and silver in melts by the visual-polythermic method. Another aim of the investigation was the clarification of the influence of exchange of anions: Substitution of I^- in a system with stratification of Li, Ag‖Cl, I [4] and of NO_3^- in a system with stratification of Li, Ag ‖Cl, NO_3 by the SO_4^{--} ion.

* Equimolar percentages of the added component.

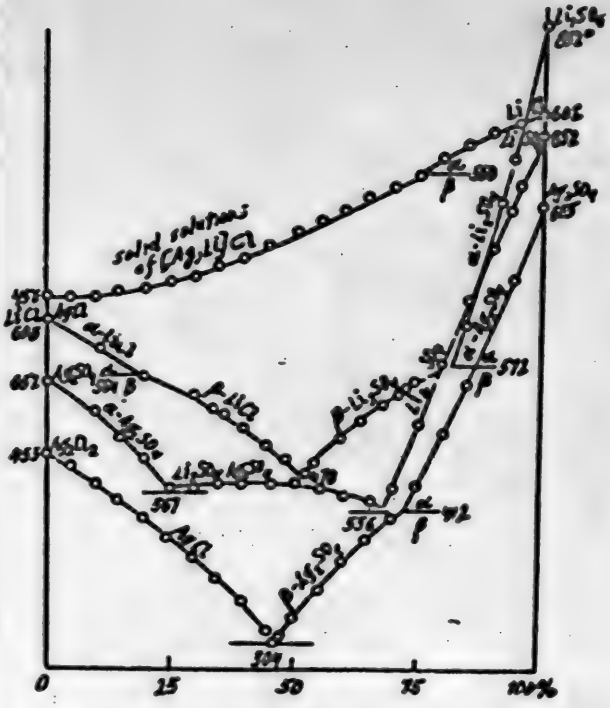

Fig. 1. Sides of the square of the reciprocal system.

Diagonal sections (Fig. 2). The thermal effect of the reaction $Li_2Cl_2 + Ag_2SO_4 \longrightarrow Ag_2Cl_2 + Li_2SO_4$ is equal to 17.8 kcal per equivalent. The stable diagonal section Ag_2Cl_2—Li_2SO_4 has the character of a binary system with a eutectic at 44.5° and 0.4% lithium sulfate. The components of the stable pair possess extremely limited reciprocal solubility in the fused state—the interval of stratification extends from 2 to 98.8% lithium sulfate at 818°. The melting curve is broken by a straight line parallel to the composition axes, due to a three-phase monotectic process. The curve is represented by a broken line up to 26% Li_2SO_4, consequent upon the experimental difficulty of determination of the crystallization temperatures of very fine drops of lithium sulfate.

The melting diagram of the unstable section of Li_2Cl_2—Ag_2SO_4 consists of six crystallization branches: α,β-continuous solid solutions [Ag, Li]Cl, β,α-sulfates of lithium, and β,α-sulfates of silver which are intersected respectively at 564° and

In the interval from 22.5% Ag_2SO_4 at 492° to 72.5% Ag_2SO_4 at 518° the melt separates into two liquid phases

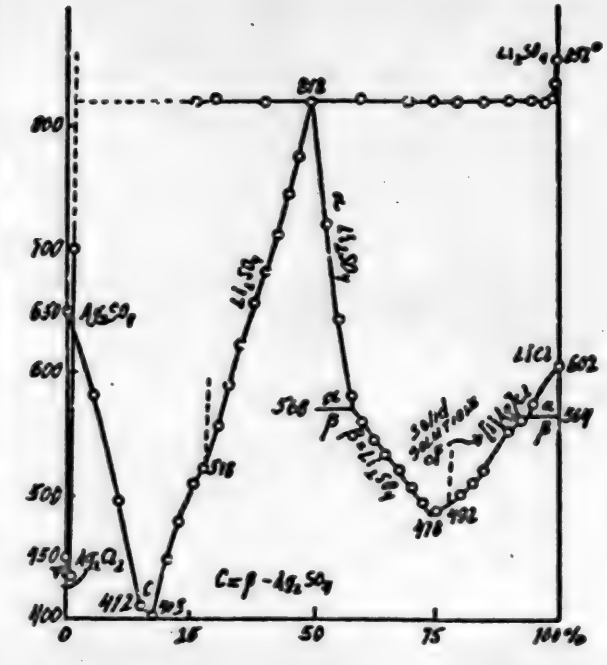

Fig. 2. Diagonal sections.

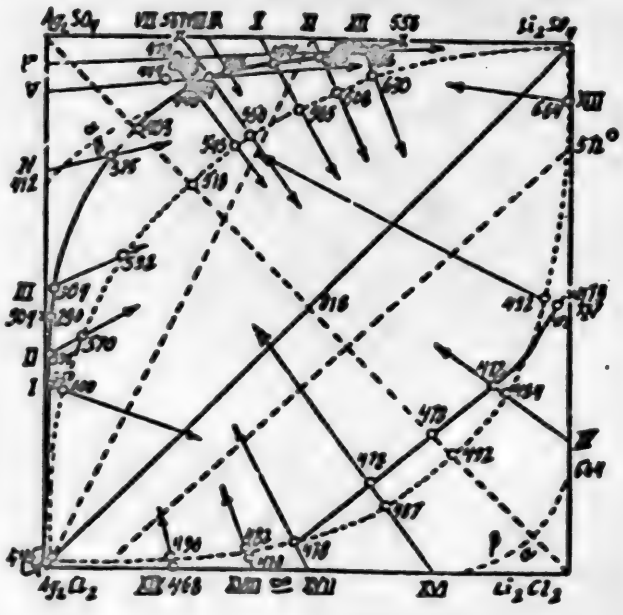

Fig. 3. Directions of internal sections.

Reciprocal system. The surface of primary separations of crystals was investigated with the help of nineteen internal sections whose directions are shown in Fig. 3. a short characterization of each of them is given in the summary table and in Figs. 4 and 5.

TABLE 2

Summary Table of Internal Sections of the Reciprocal System

No. of section	Initial mixture of components	M.p. of starting mixture	Added component	Branch I	Intersections of I and II		Branch II	Intersections II and III		Branch III	Start of stratification		
					%	t°		%	t°		%	t°	
I	65% Ag_2Cl_2+35% Ag_2SO_4	358	Li_2Cl_2	Ag_2Cl_2	0.5	358	Li_2SO_4				3	600	4
II	60% Ag_2Cl_2+40% Ag_2SO_4	340	Li_2SO_4	Ag_2Cl_2	0.5	334	Li_2SO_4				7.5	570	4
III	47.5% Ag_2Cl_2+52.5% Ag_2SO_4	338	Li_2SO_4	β-Ag_2SO_4	1.5	304	Li_2SO_4				15	532	4
IV	25% Ag_2Cl_2+75% Ag_2SO_4	432	Li_2SO_4	α-Ag_2SO_4	2.5	412	β-Ag_2SO_4	12.5	375	Li_2SO_4			4
V	10% Ag_2Cl_2+90% Ag_2SO_4	550	Li_2SO_4	α-Ag_2SO_4	22.5	444	Compound Ag_2SO_4·Li_2SO_4	30	444	Li_2SO_4			4
VI	5% Ag_2Cl_2+95% Ag_2SO_4	600	Li_2SO_4	α-Ag_2SO_4	25	479	Compound Ag_2SO_4·Li_2SO_4	62.5	526	Li_2SO_4			
VII	80% Ag_2SO_4+20% Li_2SO_4	590	Li_2Cl_2	α-Ag_2SO_4	5.5	458	Compound AB	9	440	Li_2SO_4	20	545	4
VIII	75% Ag_2SO_4+25% Li_2SO_4	570	Li_2Cl_2	Ag_2SO_4·Li_2SO_4	7.5	443	Li_2SO_4				18	550	4
IX	70% Ag_2SO_4+30% Li_2SO_4	570	Li_2Cl_2	Compound Ag_2SO_4·Li_2SO_4	6	456	Li_2SO_4						4
X	60% Ag_2SO_4+40% Li_2SO_4	573	Li_2Cl_2	Compound Ag_2SO_4·Li_2SO_4	5	474	Li_2SO_4				13.5	585	4
XI	50% Ag_2SO_4+50% Li_2SO_4	575	Li_2Cl_2	Compound Ag_2SO_4·Li_2SO_4	3.5	500	Li_2SO_4				10	608	5
XII	40% Ag_2SO_4+60% Li_2SO_4	567	Li_2Cl_2	Compound Ag_2SO_4·Li_2SO_4	2	522	Li_2SO_4				7	630	5
XIII	90% Li_2SO_4+10% Li_2Cl_2	664	Ag_2SO_4	α-Li_2SO_4							1	664	5
XIV	50% Li_2SO_4+50% Li_2Cl_2	492	Ag_2SO_4	Solid solutions [Ag, Li]Cl	2.5	478	β-Li_2SO_4	22.5	572	α-Li_2SO_4	5	492	5
XV	25% Li_2SO_4+75% Li_2Cl_2	554	Ag_2SO_4	Solid solutions [Ag, Li]Cl	14	478	β-Li_2SO_4				12.5	484	5
XVI	25% Ag_2Cl_2+75% Li_2Cl_2	554	Ag_2SO_4	Solid solutions [Ag, Li]Cl	16.5	478	β-Li_2SO_4	35	572	α-Li_2SO_4	12.5	487	5
XVII	50% Ag_2Cl_2+50% Li_2Cl_2	509	Ag_2SO_4	Solid solutions [Ag, Li]Cl	5	478	β-Li_2SO_4				5	478	5
XVIII	60% Ag_2Cl_2+40% Li_2Cl_2	491	Ag_2SO_4	Solid solutions [Ag, Li]Cl	2.5	478	β-Li_2SO_4				3	482	5
XIX	75% Ag_2Cl_2+25% Li_2Cl_2	468	Ag_2SO_4	Solid solutions (Ag, Li]Cl	0.5	465	β-Li_2SO_4				1	490	5

• Percent of additive.

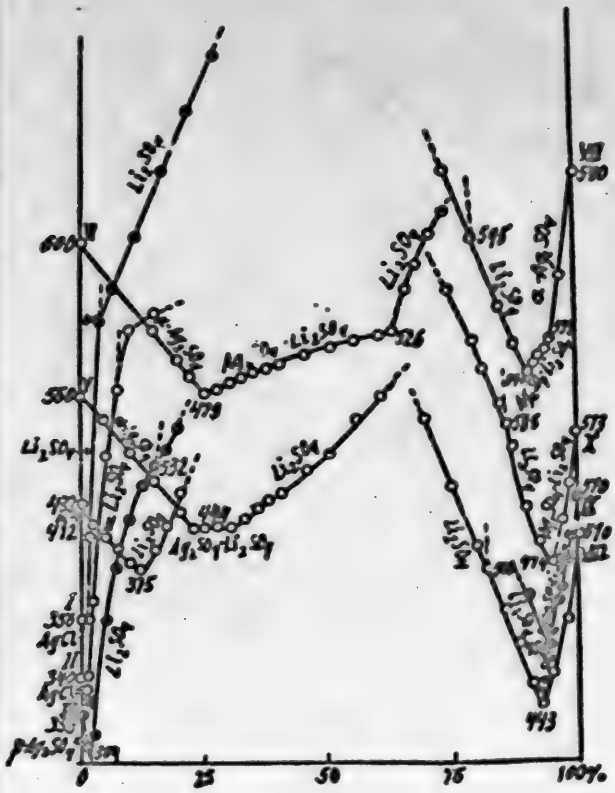

Fig. 4. Internal sections I–X.
I–65% Ag_2Cl_2 + 35% Ag_2SO_4 → Li_2Cl_2; II-60% Ag_2Cl_2 + + 40% Ag_2SO_4 → Li_2SO_4; III-47.5% Ag_2Cl_2+52.5% Ag_2SO_4 → Li_2SO_4. IV-25% Ag_2Cl_2 + 75% Ag_2SO_4 → Li_2SO_4 V-10% Ag_2Cl_2 + 90% Ag_2SO_4 → Li_2SO_4; VI-5% Ag_2Cl_2 + 95% Ag_2SO_4 → Li_2SO_4; VII-80% Ag_2SO_4 + 20% Li_2SO_4 → → Li_2Cl_2; VIII-75% Ag_2SO_4 + 25% Li_2SO_4 → Li_2Cl_2; IX-70% Ag_2SO_4 + 30% Li_2SO_4 → Li_2Cl_2; X - 60% Ag_2SO_4 + 40% Li_2SO_4 → Li_2Cl_2; M = α-Ag_2SO_4; N = β-Ag_2SO_4.

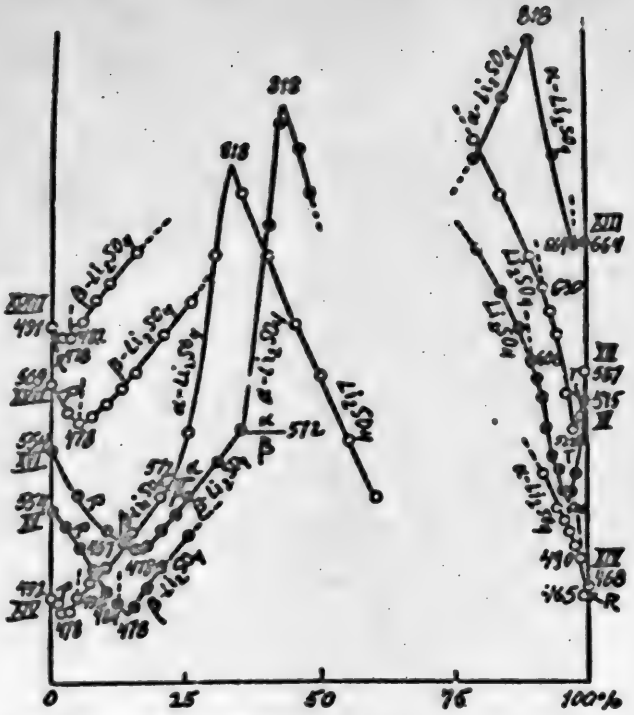

Fig. 5. Internal sections XI–XIX.
XI-50% Ag_2SO_4 + 50% Li_2SO_4 → Li_2Cl_2;
XII-40% Ag_2SO_4 + 60% Li_2SO_4 → Li_2Cl_2;
XIII-90% Li_2SO_4 + 10% Li_2Cl_2 → Ag_2SO_4;
XIV-50% Li_2SO_4 + 50% Li_2Cl_2 → Ag_2SO_4;
XV-25% Li_2SO_4 + 75% Li_2Cl_2 → Ag_2SO_4;
XVI-25% Ag_2Cl_2 + 75% Li_2Cl_2 → Ag_2SO_4;
XVII-50% Ag_2Cl_2 + 50% Li_2Cl_2 → Ag_2SO_4;
XVIII-60% Ag_2Cl_2 + 40% Li_2Cl_2 → Ag_2SO_4;
XIX-75% Ag_2Cl_2 + 25% Li_2Cl_2 → Ag_2SO_4.
R - Solid solutions (Li, Ag) Cl; T - $Ag_2SO_4 \cdot Li_2SO_4$.

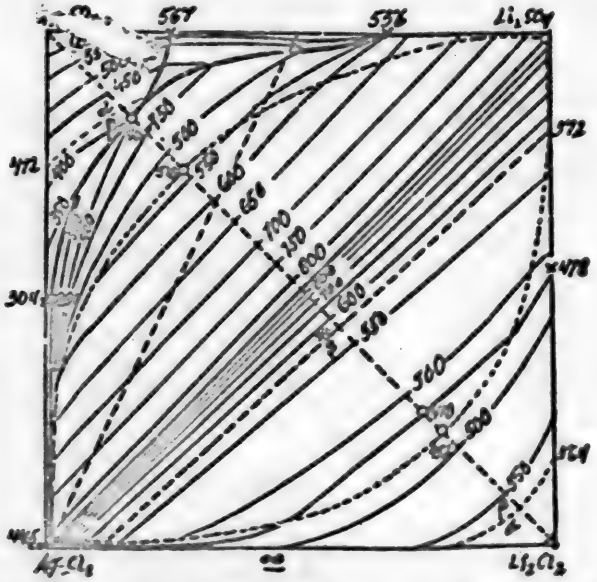

Fig. 6. Projection of isotherms on to the square of compositions.

The singular temperature maxima of all the sections are at the points of their intersection with the stable diagonal section. The results of measurements are generalized in the form of a projection of the isotherms on to the square of compositions of the reciprocal system (Fig. 6). The positions of the invariant points, of the lines of joint crystallization of components, and of the lines demarcating the stratification region are represented in the form of projections of those points and of the lines of the ternary system Ag_2Cl_2–Li_2SO_4–Li_2Cl_2 on to the AgCl–LiCl side (Fig. 7) a. of the lines of the ternary system Ag_2Cl_2–Li_2SO_4–Ag_2SO_4 on to the Li_2SO_4–Ag_2SO_4 side (Fig. 8).

On the projections are also represented the three-phase and four-phase monotectic equilibrium (ab and cd in Fig. 7 and ab in Fig. 8) and the polymorphic transformation

of lithium sulfate (broken line).

We see from Fig. 6 that the system consists of eight fields of crystallization: α, β- lithium sulfates occupying 75.6%, α, β-solid solutions of [Ag, Li]Cl (15.3%); α, β-sulfates of silver (6.5%); compound $Ag_2SO_4 \cdot Li_2SO_4$ (2.2%) and silver chloride 0.4% of the total area of the square.

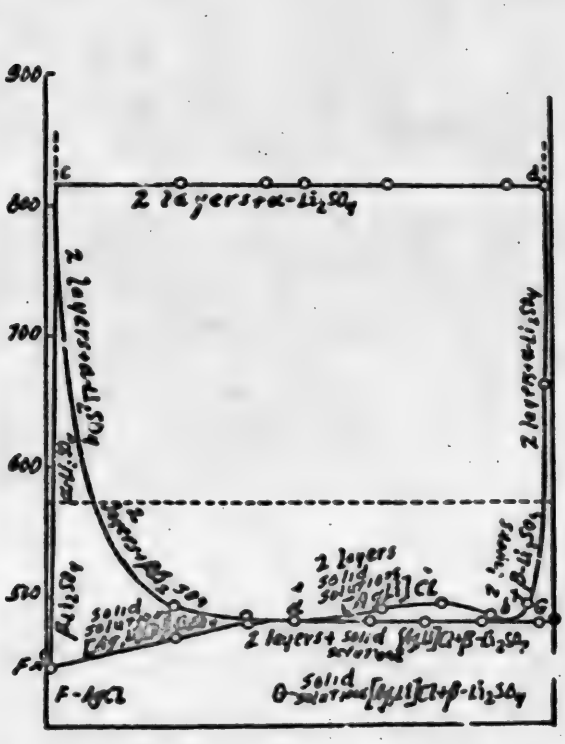

Fig. 7. Projection of the ternary system Ag_2Cl_2–Li_2SO_4–Li_2Cl_2 on to the AgCl–LiCl side.

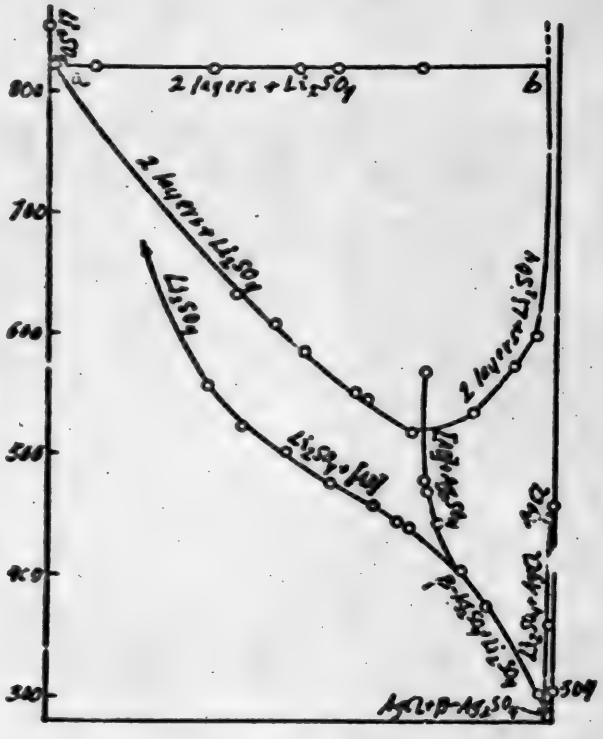

Fig. 8. Projection of the ternary system Ag_2Cl_2–Li_2SO_4–Ag_2SO_4 on to the Li_2SO_4–Ag_2SO_4 side.

The stable diagonal section Ag_2Cl_2–Li_2SO_4 cuts the square of the reciprocal system at two ternaries: Ag_2Cl_2–Li_2SO_4–Ag_2SO_4 with a ternary eutectic melting at 290°. In the same system is found the transient compound $Ag_2SO_4 \cdot Li_2SO_4$. Ag_2Cl_2–Li_2SO_4–Li_2Cl_2 with solid solutions of [Ag, Li]Cl. The region of stratification occupies 65.2% of the total area of the square of compositions. Its greater part lies in the lithium sulfate field and only a very minor portion in the field of solid solutions of [Ag, Li]Cl. On the line of joint crystallization of the compounds in question, a four phase monotectic process takes place in the stratification region at 478°.

The compound $Ag_2SO_4 \cdot Li_2SO_4$, which is congruent on the outer side, becomes incongruent inside the system with a "transition" point at 412°; it decomposes on melting under the influence of silver chloride and of the stratification region. It does not enter into the composition of the phase complexes of the solidifying melts.

SUMMARY

1. The ternary reciprocal system of the chlorides and sulfates of lithium and silver has been investigated in melts by the visual-polythermic method of physicochemical analysis. The system belongs to the singular irreversibly reciprocal type of system with stratification of melts, i.e., to the third class of the classification of A.G. Bergman and Dombrovskaya.

2. The reciprocal system $Li, Ag \parallel Cl, SO_4$ is characterized by a well-marked singularity with a sharp unilateral shift of equilibrium in the direction of silver chloride and lithium sulfate due to the extremely limited reciprocal solubility of these salts in the melted state and to the high thermal effect of the reaction $Li_2Cl_2 + Ag_2SO_4 \longrightarrow Li_2SO_4 + Ag_2Cl_2$, which is equal to 17.80 kcal per equivalent.

3. The stable diagonal section is a singular plane in which intersection occurs of the isotherm and boundary of stratification of the ternary systems Ag_2Cl_2–Li_2SO_4–Ag_2SO_4 and Ag_2Cl_2–Li_2SO_4–Li_2Cl_2 at an acute angle.

4. The investigation of the reciprocal system Li, Ag‖Cl, SO_4 has provided further support for the hypothesis that stratification in the fused state in the majority of cases is the consequence of a differing structure of the outer electron shells of the ions and of the resultant sharp difference in their polarization characteristics and in the physicochemical properties of the components of the stable pair.

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Received November 3, 1952

A STUDY OF PHOSPHOMOLYBDIC AND SILICOMOLYBDIC COMPLEXES IN SOLUTION

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Many investigations have been made of the composition and structure of heteropoly compounds in the solid state; recently a series of interesting studies has been published by E. A. Nikitina and co-workers [1]. These give little information, however, about the equilibria in solution, the formation conditions, and the stability of the heteropoly compounds in solution. B. V. Nekrasov [2] considers the interaction of caustic alkali with heteropoly acids as a process of gradual breakdown of the complex acid; E. A. Nikitina [3] assumes that the solid phase formed in this way consists of solid solutions (limitedly saturated and unsaturated) of heteropoly compounds. A very significant factor for characterization of the use of heteropoly acids in chemical analysis is the formation and stability of these acids in dependence on the hydrogen ion concentration. In this connection the molybdic acid complexes with different central atoms are characterized by a number of features which make possible the separate determination of silicon, phosphorus, etc. in mixtures. These heteropoly compounds exhibit these well-marked specific effects when reacted with various anions which bind molybdenum into a complex. Existing data for the structure and properties of the crystalline compounds do not account for this difference in the properties of heteropoly acids containing different central atoms. Thus, for example, Pauling [4] considers that the central atom occupies a certain free space in the lattice composed of atoms of molybdenum and oxygen and molecules of H_2O. We know, however, that the central atom often governs the most important properties of heteropoly acids. It is clear that the characteristics of the conditions of formation of heteropoly acids, their stability and a series of individual properties can only be established by study of the equilibria of formation in solution. This approach can be made most effectively by the method of physicochemical analysis.

This method was adopted by I. V. Tananaev [5] in a study of silicomolybdic acid in which determinations were made of the composition of the complex in solution and of the dependence on the molybdate concentration and on the acidity of the solution. Tananaev, however, only studied equimolecular mixtures in which equality existed between the sums of the concentrations of the three components: sum of SiO_2, MoO_3 and H_2SO_4 = 0.025 mole/l. In the practice of colorimetric analysis, however, considerably larger excesses of acid and molybdate are employed.

The objective of the present investigation was the study of the equilibria, formation conditions and stability of phosphomolybdic and silicomolybdic acids in solutions; the principal method of investigation was physicochemical analysis.

General characterization of the conditions of equilibrium in the system phosphate (silicate)-molybdate-acid. We applied physicochemical analysis to the investigation of the equilibrium (reversible) systems. It may be noted, however, that certain properties of the solutions of the reacting components clearly indicate irreversibility of the reactions in certain conditions

The state of molybdenum in acidified solutions of ammonium molybdate has hitherto not been adequately studied. Investigation of various characteristics of molybdic acid solutions (depression of freezing point, diffusion coefficients, dialysis, etc. [6,7,8]) has revealed the presence in acid solutions of various forms of polymerized molybdic acid ions. Thus, for instance, simple ions of MoO_4^{--} are found in molybdate solution in an alkaline medium and when the pH is reduced to 6.5. Further drop in the pH from 5.0 to 1.5 leads to formation of hexamolybdates, and still greater acidification leads to dodecamolybdates. At the same time the possibility is not excluded of formation of trimolybdate ions when the pH of the solutions is 6.5-5.0. At the same time there are various theories of the nature of the coordinated groups in heteropoly acids; thus the composition of phosphomolybdic acid, as we know it, is represented by the formula $H_7[P(Mo_2O_7)_6]$ or $H_3[P(Mo_3O_{10})_4]$. Consequently phosphomolybdic acid may exist in equilibrium with dimolybdate or trimolybdate ions. Since a higher degree of polymerization of molybdate is probable in strongly acid solutions, while the speed of depolymerization is unknown, the formation is possible of systems which are not in equilibrium, and the method of physicochemical analysis may prove to be inapplicable.

We know also that due to the colloidal character of solutions of silicic acid, the conditions of formation and breakdown of silicomolybdic acid exhibit a series of peculiarities [9]. We know that in the colorimetric determination of silicon in presence of phosphorus, use is made sometimes of strongly acid solutions, the silicomolybdate

complex being stable while the phosphomolybdic complex decomposes. In other cases the test solution is first acidified and after a short period addition is made of molybdate; in these conditions a silicomolybdic complex is not formed. Consequently in the case of solutions of silicomolybdic complexes the absence of equilibrium may result (apart from the factors mentioned above) from the colloidal character of silicic acid in solutions. This fact clearly calls for a preliminary study of the general characteristics of equilibrium in the system.

The following starting solutions were used: 1) Solution of ammonium molybdate containing 0.1 mole MoO_3 per liter. 2) 0.1 molar solution of sodium silicate or sodium phosphate. 3) 0.2 N nitric acid solution. These solutions were mixed in various ratios and in various orders with variation of the period between mixing of two components and introduction of the third component. Mixing of the three components was followed by determination of the optical density of the solutions after intervals of 10 minutes and 1, 4 and 24 hours.

Omitting the experimental details, we may note the following results: In most cases the optical density of the solution was identical for solutions of phosphomolybdic complexes, regardless of the order of mixing and of the time within the limits of the following concentrations: $[PO_4^{---}] = 2 \cdot 10^{-4}$, $[MoO_4^{--}]$ from $24 \cdot 10^{-4}$ to $324 \cdot 10^{-4}$ and pH of 0.7 to 2.0. The experimental data consequently supply evidence of sufficiently complete reversibility of the system.

The data for solutions of the silicomolybdic complex revealed poor reversibility of the processes and a considerable dependence of the optical density of the solutions on the order of mixing and on the period of standing. The most reproducible results were obtained in the following conditions: To a solution of silicate was added distilled water, followed by the required amount of acid, and immediately after mixing, this was followed by ammonium molybdate solution. This order of mixing of the reacting substances was also followed in the experiments described in the subsequent sections of this paper. Approximately the same optical density was obtained by adding the molybdate to the acidified silicate and holding for a short period; also by adding the silicate solution to the acidified molybdate solution. But if the silicate and molybdate solutions were first mixed together and then the acid added, the results were poorly reproducible. The optical density of all the solutions changes with time. At the start the color is intensified but afterwards it weakens, due to gradual irreversible decomposition of the silicomolybdic complex with formation of colloidal silicic acid in a form that does not react with molybdate. In Table 1 are presented some experimental results. The solutions were prepared as described above. The color intensity was determined by comparison of the test solutions with a borax-containing K_2CrO_4 solution.

TABLE 1

Silicate Concentration: $2 \cdot 10^{-4}$ mi

Molybdate conc.	$24 \cdot 10^{-4}$			$124 \cdot 10^{-4}$			$224 \cdot 10^{-4}$			
pH of solution	2.0	1.3	0.7	2 0	1.3	0.7	2.0	1.3	0.7	0.3
Period of standing	Color corresponds to a solution containing following amount of chromate (in mg/l)									
10 minutes.	30	8	0	70	35	26	70	70	60	2
1 hour. . . .	38	18	1	70	85	58	75	75	75	4
4 hours . . .	34	22	1	56	80	80	56	60	70	6
24 hours . .	18	20	1	40	60	60	30	44	56	12

The experimental results show that with increasing acidity of the solution there is an increase in the period necessary for maximum formation of the colored complex. Increasing concentration of molybdate cuts down this period but does not bring about complete stability of the complex; in all cases the complex is appreciably decomposed at a pH of 2 to 1.3 after 24 hours.

The influence of temperature must be considered in connection with the question of equilibrium in the system. Solutions were heated in test tubes to 60° and they were compared in the hot state with standard chromate solutions. The color intensity of solutions of phosphomolybdic complex increases 3-10 times at 60° (depending on the Mo/P ratio) in comparison with the same solutions at 20°; after cooling to 20° the color intensity of the solutions again falls to the initial value. The color intensity of solutions of the silicomolybdic complex in some cases also increases when heated. On cooling, however, the intensity does not fall to the original value and the period of stability of solutions of silicomolybdic complex is shortened.

Strickland [10] observes that the optical density of freshly prepared solution of silicomolybdic acid falls by approximately a factor of 2 after 24 hours. He attributes this to formation of an isomer of unknown structure. In an examination of solutions of silicomolybdic complex at various values of pH and various concentrations of excess molybdate, we did not observe any stable products of decomposition or isomerization of silicomolybdic complex in solution.

The above results show that the processes are reversible in solutions of phosphomolybdic complexes; conversely, irreversible processes are observed in silicomolybdic solutions, associated with passage of silicic acid into the colloidal state. Consequently physicochemical analysis, when applied to the formation of the silicomolybdic complex, can only give approximate results. In all cases the solutions containing a molar ratio of phosphorus (or silicon) to molybdenum of 1:12 have a much lower optical density than solutions with a large excess of molybdate. This fact points to appreciable dissociation of the complex.

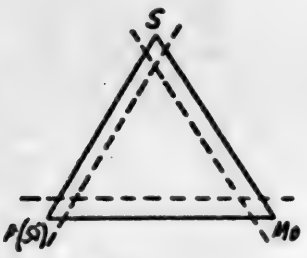

Fig. 1.

Examination of equimolecular mixtures. Determination of the composition of the complex in solution when the stability is low (appreciable dissociation) is most conveniently carried out by a study of the properties of mixtures containing a constant total of molar concentrations of reactants. Phosphomolybdic and silicomolybdic complexes are formed by reacting phosphate (or silicate) with molybdate in an acid medium. Nitric, hydrochloric or sulfuric acids, however, do not enter into the composition of the complexes according to the available data; nor do hydrogen ions enter into the coordination sphere since heteropoly acids are strong acids. Evidently a certain degree of acidity of the solution influences the degree of polymerization of the molybdic acid ion. We therefore considered it would be expedient to perform some series of experiments at various pH values, but with maintenance only of a constant sum of the phosphate (or silicate) and molybdate while keeping the pH of the solutions constant.• On this basis a study was made of complexes in a system of two reactants in solution. The system may be represented by a triangle of composition: The central ion [P(Si)], the coordinated ion (Mo) and the solvent (S) (Fig. 1). Equimolecular mixtures correspond to sections of the triangle of composition parallel to the side P(Si)—Mo.

Experiments for various equimolecular mixtures containing an identical molar ratio of the coordinated ion to the central ion Mo/P(Si) corresponded to sections through the apex of the triangle and the appropriate point on the side P(Si)—Mo.

Other sections are described in later parts of this paper. The usual form of graphical representation of the results of physicochemical analysis are unsatisfactory in the present case because the composition of the obtained colored compounds diverges sharply from the 1:1 ratio. Consequently, on the ordinates we have marked directly the P/Mo ratio in the range of 1 to 50. By this means the middle of the abscissas corresponds not to the ratio P:Mo = 1:1 (as in the usual diagram) but to the ratio P:Mo =1:25.

In Fig. 2 are shown the results of several series of experiments. Constancy was maintained of the sum of the molar concentrations of phosphorus and molybdate in each series, and the acidity of the solution was also held at a constant value. Acidification was effected with sulfuric acid; the normality of the solution in terms of sulfuric acid is specified for each series of experiments below Fig. 2. The optical density was measured on a FM photometer using a light filter with an effective wave length of 465 mμ.

Examination of the plots on the diagram shows that in each series of experiments there is a maximum in the optical density, which indicates the formation of one colored complex compound in the given series. The maximum in each series is observed at a different molar ratio of phosphate to molybdate in solution. For those series of experiments in which the acidity was $[H^+]$ = 0.03-0.085 N, the maximum of optical density corresponds to the ratio P:Mo = 1:24, at an acidity of 0.2 N it corresponds to P:Mo = 1:19 (the optical density at P:Mo = 1:12 and 1:24 differs slightly from the maximum); in weakly acid solutions (0.01 N) the maximum of optical density corresponds to P:Mo = 1:12. The correlation of the maximum of optical density of solutions with series of solutions of differing ratios of P:Mo points to formation of complexes of different compositions.

• Concerning the suitability of physicochemical analysis for the investigation of such systems, we may note that the condition of equimolarity of a series of solutions is also to some extent arbitrary in view of the undoubted (if not accurately known) polymerization of molybdate. Consequently, apart from other reasons, we believe it is necessary not to limit ourselves to the examination of equimolecular solutions but to also investigate other ratios (see the later sections).

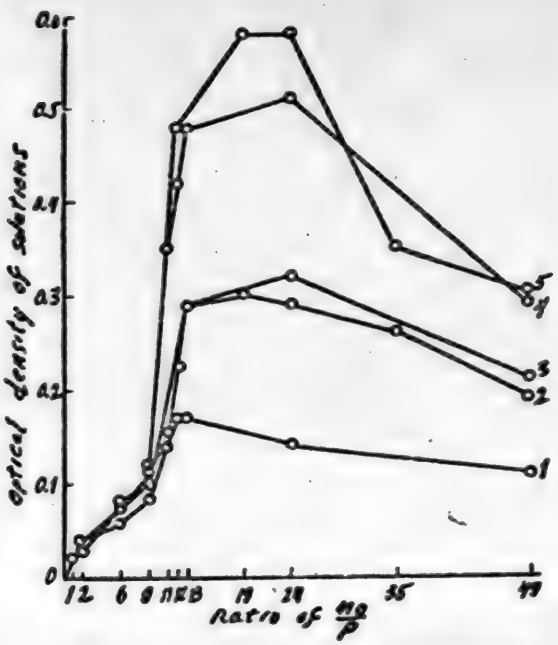

Fig. 2. Normality of the solution with respect to sulfuric acid: 1) 0.01 N, 2) 0.02 N, 3) 0.085 N, 4) 0.03 N, 5) 0.07 N.

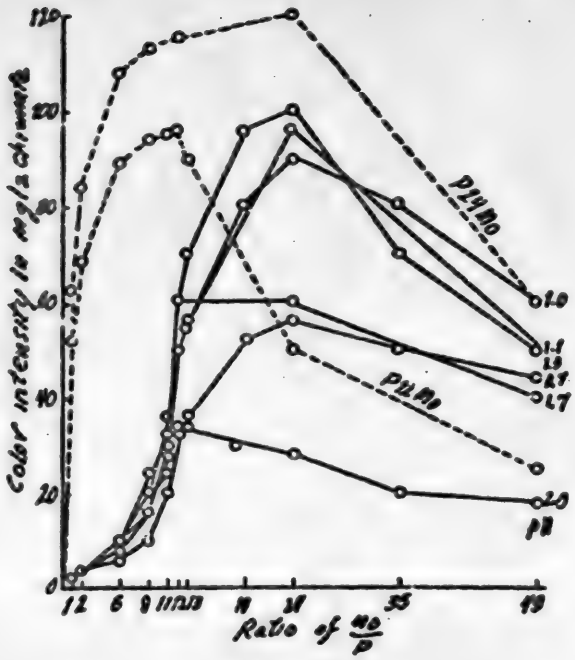

Fig. 3.

The optical density is seen to drop sharply in all the series of experiments with a P:Mo ratio greater than 1:12, indicating the formation in these experimental conditions of a colorless complex compound containing less than 12 atoms of molybdenum per atom of phosphorus.

In Fig. 3, are plotted the results of some series of experiments, with a constant sum of concentration of molybdate and phosphate in solution of $1.25 \cdot 10^{-4}$ mole/l. The various series differed only in respect to the pH of the solution. The pH values of individual series ranged from 0.7 to 2.0. Nitric acid was the acidifying agent. The color intensity of the solutions was measured by comparison with a series of standards consisting of potassium chromate and borax. In the diagram the curves corresponding to the color intensity of the experimental solutions are represented by solid lines. The broken lines represent the color theoretically calculated for the case of complete bonding of phosphate in complex compounds containing 12 to 24 atoms of molybdenum per atom of phosphorus.

Inspection of the curves reveals, as in the above-described experiments, that at higher acidities (pH = 0.7-1.3) the maximum color of the solutions occurs at ratios of P:Mo = 1:24, and that at pH = 2.0 the color maximum occurs at a ratio of 1:12. The greatest distance between the solid and the broken lines occurs in the portion of the diagram to the left of the maximum of intensity, which confirms the formation of a colorless complex when there is excess of phosphate in the solution. The distance between the solid lines corresponding to the experimental data for pH values of 0.7 to 1.3 and the broken line corresponding to the color theoretically calculated* for the case of complete binding of phosphate into the colored complex with a ratio of P:Mo = 1:24 decreases with increasing molybdate content. A similar dependence is found for the curves at pH = 2 for the theoretically calculated color in the condition of complete bonding of phosphate in the colored complex with a ratio of P:Mo = 1:12. Hence with increasing excess of molybdate in the solution, no new complexes are formed, and more complete linking of phosphate to the colored complex is observed.

The following main conclusions can be drawn from the described experiments. The maximum of optical density of equimolecular mixtures of phosphate and molybdate at a pH of about 2 is observed with a ratio of

*Calculation was performed on the basis of the value of the molar absorption coefficient measured in presence of a considerable excess of molybdate.

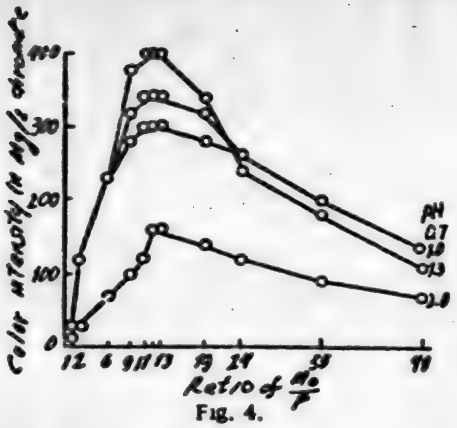

Fig. 4.

P: Mo = 1:12, and in a series of cases with pH of 0.7 to 1.3 the maximum is at P: Mo = 1:24. The latter results justify the inference that in certain conditions a more complex phosphomolybdic acid, containing 24 atoms of molybdenum per atom of phosphorus, is formed. The formation of such compounds may be correlated with the higher degree of polymerization of molybdate in acid solutions. Since the degree of polymerization of molybdate is not known at present with sufficient reliability, the above results may be regarded as preliminary (see also the observation on p. 391). It is significant, however, that in the system silicate–molybdate (see below) the maximum of optical density in equimolecular mixtures corresponds only to the ratio Si: Mo = 1:12. Moreover, as was remarked above, the optical density sharply increases in the system phosphate-molybdate with rising temperature. At the same time, the position of the optical density maximum also shifts in such a manner that at a temperature of 60° in all cases the maximum corresponds to the ratio P: Mo = 1:12. Fig. 4 shows the data* obtained for equimolecular mixtures at 60°.

Results obtained for the system silicate-molybdate are presented in Fig. 5. They confirm the conclusions of I. V. Tananaev [5] about the formation in solution of a colored compound with a ratio of Si: Mo = 1:12. In view of the above data for the dependence of the color on the duration and order of mixing of the solutions, experiments were carried out in the following way: Acid was added to the dilute solution of silicate, mixing was performed and immediately after that the molybdate was added. The optical density of the solutions was measured after 10 minutes and 1, 4 and 24 hours.

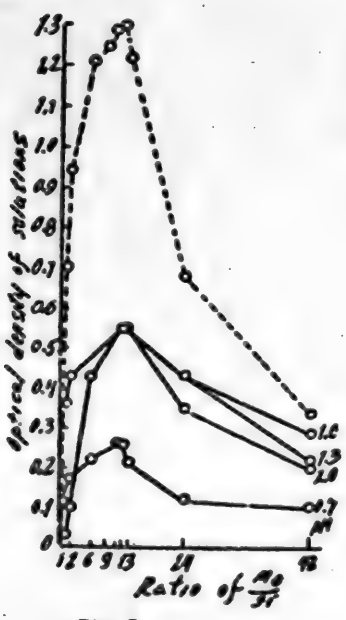

Fig. 5.

The maximum of optical density is much lower in solutions of the silicomolybdic and of the phosphomolybdic complexes than the value calculated for the conditions of full binding (see the broken and solid lines in Figs. 3 and 5). This signifies appreciable dissociation or partial irreversible decomposition of the complex in the absence of excess of molybdate. This inference was checked by experiments using a solution of phosphomolybdic acid previously isolated in the pure form. When a 10^{-3} molar solution of the acid was twice diluted, the optical density fell by a factor of 3, which confirms the fall in the number of absorbing light centers on dilution. The same result was obtained in the case of presence of sulfuric acid in a phosphomolybdic acid solution. Introduction of excess of acidified solution of molybdate intensifies the optical density of the solutions.

Concerning the effect of pH, the foregoing data make it clear that at pH = 2 the formation of colored compounds is intensified, but at higher acidities (pH = 0.7 and less) the color of solutions of phosphomolybdic acid is less intense. A certain optimum acidity of solution is also observable with the silicomolybdic complex but the dependence is a more complex one due to the irreversibility of the process.

Study of solutions with constant concentration of the central ion and variable concentration of the coordinated ion. These solutions correspond to the section of the triangle of composition along lines parallel to the side S–Mo. This section permits the determination of the degree and character of the effect of excess of the coordinatable ion which is the reactant in the conditions of colorimetric analysis. Some data for the phosphomolybdic complex are given in Table 2.

The results show that with increasing concentration of molybdate the color intensity increases but subsequently remains nearly constant, this stage corresponding to complete binding of the phosphate in the colored complex. At a pH of about 1.7-2.0 with a very large excess of molybdate, the color weakens, evidently due to

* The data were obtained by comparing the heated solutions with standard solutions of chromate (these were not heated), because measurement of optical density at 60° is inconvenient with the help of a photometer.

TABLE 2

Prep. No.	Molar conc. of molybdate $C_{Mo} \cdot 10^4$	Molar conc. of phosphate $C_p = 1.0 \cdot 10^{-4}$					$C_p = 2.0 \cdot 10^{-4}$				
		pH of solution									
		2.0	1.7	1.3	1.0	0.7	2.0	1.7	1.3	1.0	0.7
		corresponds to color of chromate (mg/l)									
1	48	8	14	16	10	–	12	24	24	16	8
2	88	8	14	20	24	–	16	30	36	38	28
3	124	8	14	24	22	–	16	28	40	44	40
4	224	8	12	24	28	28	12	24	36	48	50
5	324	6	8	24	26	26	12	16	38	48	52

secondary processes developed under the influence of anions of the acids which were introduced into the solution for the purpose of acidification. Binding of the greater part of the phosphate in the colored complex at pH = 1 necessitates a molybdate excess of approximately 0.01 mole/l. Very similar results were obtained in other series of experiments with acidification of a solution of phosphate and molybdate, also with mixtures of phosphomolybdic acid with excess of molybdate. Consequently the phosphomolybdic complex is appreciably dissociated in the absence of excess of molybdate.

For the characterization of the stability of heteropoly acids, interest attaches to determination of the equilibrium constant of the reaction between the central and the coordinatable ion. This determination cannot be performed accurately since the degree of polymerization of molybdate in solution is unknown. On the basis of experimental data we can calculate the concentration of phosphate bound into the complex ($[PO_4Mo_x]$) from measurements of the optical density, also the concentration of molybdate ($[Mo_{free}]$) not bound to the colored complex and that of the phosphate ($[PO_{4free}]$) not bound to the colored complex; the last two magnitudes are calculated from the difference between the total concentration of the respective ions and the concentration of the colored complex. Such a calculation, however, must be regarded as approximate due to the following two facts: a) The phosphate and molybdate not bound into the colored complex can partly exist in solution in the form of colorless complexes; b) the molybdate not bound into the complex is present in a polymerized form; thus, if the total number of coordinated atoms of molybdenum is equal to $x = n \cdot m^*$, then the equilibrium in general may be represented by the scheme**;

$$PO_4Mo_{n \cdot m} \rightleftarrows PO_{4free} + n\,Mo_m \qquad (1)$$

A study of the shift of equilibrium with changing concentration of molybdate can, evidently, only permit us to calculate the value of n, since this term determines the degree of influence of molybdate on the equilibrium shift of the formation of the colored complex.

In accordance with equation (1) we can write the equilibrium expression:

$$K_{complex} = \frac{[PO_{4free}][Mo_m]^n}{[PO_4 \cdot Mo_x]} \qquad (2)$$

Putting (2) into logarithmic form, we get:

$$\log K_{complex} = n \log [Mo_m] + \log \frac{[PO_{4free}]}{[PO_4 \cdot Mo_x]} \qquad (3)$$

Putting $\log K_{complex} = a$ (constant), we get:

$$n \log [Mo_m] = a + \log \frac{[PO_4 \cdot Mo_x]}{[PO_{4free}]} \qquad (4)$$

The ratio $[PO_4 \cdot Mo_x]:[PO_{4free}]$ is determined from experimental data and characterizes the degree of bonding of phosphate in the colored complex. This ratio depends on the concentration of the excess of molybdate: a p-fold change in the molybdate concentration results, in accordance with equation (2), in the ratio of bound to unbound phosphate changing by a factor of p^n; in this way we can calculate the magnitude of n, i.e., the coefficient in equation (1). This calculation is more conveniently performed on the basis of equation (4): if we plot (in identical scales) on the abscissas the values of $\log [Mo_{free}]$ and on the ordinates the values of $\log [PO_4 \cdot Mo_x]/[PO_{4free}]$, then the tangent of the angle of slope will be equal to the value of n. Some experimental

* Usually x = 12.

** Arbitrary symbols are introduced into this equation in order not to confuse the study of the equilibrium by any concepts on the basis of the study of the derived equation (1a) (see below).

and calculated values are enumerated in Table 3.

TABLE 3

Expt. No.	Molar conc. of molybdate $C \cdot 10^4$	Molar conc. of phosphate $2 \cdot 10^{-4}$, pH = 1.0						
		corresponds to color of chromate (mg/l)	$[P_{bound}]$ $C \cdot 10^4$	$\frac{[P_{bound}]}{[P_{free}]}$	$[Mo_{free}]$ $C \cdot 10^4$	$\log \frac{[P_{bound}]}{[P_{free}]}$	$\log [Mo_{free}]$	$-\log K_{complex}$
1	48	16	0.66	0.49	40.08	−0.31	−2.40	9.29
2	88	38	1.58	3.76	69.04	0.58	−2.16	9.22
3	124	44	1.83	10.8	102.04	1.03	−1.99	8.99
4	324	48	2.00	—	—	—	—	—
5	48	14	0.63	0.46	40.44	−0.34	−2.39	9.22
6	88	36	1.63	4.40	68.44	0.64	−2.17	9.32
7	124	40	1.82	10.10	102.18	1.00	−1.99	8.96
8	324	44	2.00	—	—	—	—	—
9	48	12	0.60	0.43	40 80	−0.37	−2.39	9.19
10	88	32	1.60	4.00	68.80	0.60	−2.16	9.24
11	124	36	1.80	9.00	102.40	0.95	−1.99	8.91
12	324	40	2.00	—	—	—	—	—

Experiments 1 to 4 were performed in presence of nitric acid, 5 to 8 in presence of hydrochloric acid, and 9 to 12 in presence of sulfuric acid.

The data of Table 3 show that a slight increase in molybdate concentration sharply shifts the equilibrium of (1). Calculation of the value of n by the above procedure gives 3.7 and 4.3 (see Fig. 6).

The presented data for the value $n \approx 4$ to some extent are consistent with the formula for phosphomolybdic acid $H_3[P(Mo_3O_{10})_4]$, and not with the formula $H_7[P(Mo_3O_7)_4]$. If we assume that dissociation of the colored complex yields free phosphate and molybdic anhydride with a polymerization factor of 3 (m = 3), then on the basis of study of the equilibrium we may express equation (1) in the form•:

$$P(Mo_3O_{10})_4^{---} \rightleftharpoons PO_4^{---} + 4(MoO_3)_3. \qquad (1a)$$

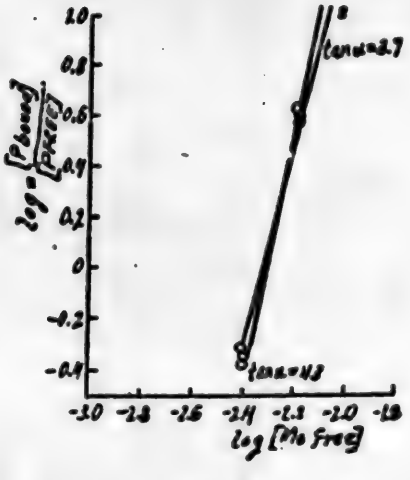

Fig. 6.

The last column of Table 3 contains the negative logarithms of the equilibrium constant of the phosphomolybdic complex calculated on the basis of $n = 4$. The equilibrium constants calculated on this assumption are sufficiently constant with a fairly large change of molybdate concentration as well as of the pH of the solution (in other experiments). On the basis, therefore, of the above data we can assume for a pH of 1.0 that:

$$K_{complex} = \frac{[PO_4^{---}]\,[(MoO_3)_3]^4}{[P(Mo_3O_{10})_4^{---}]} = 5.6 \cdot 10^{-10}.$$ The mean value is given.

This value enables us to calculate that bonding of phosphorus to the extent of 99% in the colored complex takes place at a concentration of $[Mo_{free}] = \sqrt[4]{K \cdot \frac{99}{1}} \approx 10^{-2}$. This result is in satisfactory accord with the preceding experimental data.

• The state of molybdate in strongly acid solution has not been adequately studied. Consequently the formula $(MoO_3)_3$ must be considered an arbitrary expression of the state in which it exists in the dilute molybdic liquid. The above-described experiments permit the possibility of determination of only the coefficient 4, since the equilibrium of complex formation changes in dependence on the fourth power of the concentration of the excess molybdate. The polymerization factor of 3 has not been experimentally proved, and is merely an inference from the over-all composition of the complex (12 atoms of molybdenum per atom of phosphorus) and from the coefficient 4.

A considerable shift of equilibrium is likewise observed for the silicomolybdic complex on introduction of excess of molybdate; when this excess is about $8 \cdot 10^{-3}$ molar, the optical density becomes almost constant, i.e., there is substantially complete bonding of silicic acid in the colored complex. Some data obtained 1 hour after mixing of the initial solutions are submitted in Table 4.

Hence the general character of the dependence, and also the concentration, at which a colored complex is formed is roughly the same as for the phosphomolybdic complex, although the silicomolybdic complex is distinguished by less dissociation. Data are given below for the stability of the silicomolybdic complex in presence of excess of citric acid and phosphate ion. Due to the instability of the equilibrium of formation of the silicomolybdic complex, more detailed calculations were not undertaken.

Investigation of solutions with constant concentration of molybdate and varying concentration of the central ion of the complex and comparison of the stability of the complexes. These series of experiments corresponded to the section of the composition triangle along lines parallel to the S—P(Si) side. This section permits examination of the effect of excess of central ion.

Results of experiments with the phosphomolybdic complex showed that increasing concentration of phosphate in solution up to a P:Mo ratio of more than 1:12 was accompanied by weakening of the color intensity, which indicates a shift of equilibrium in the direction of formation of a colorless complex containing less than 12 g-atoms molybdate per g-ion phosphate.

TABLE 4

Expt. No.	Molar conc. of molybdate $C \cdot 10^4$	Molar conc. of silicate $2 \cdot 10^{-4}$				
		pH of solution				
		2.0	1.3	1.0	0.7	0.3
		light absorption of solution $\log \frac{I_0}{I}$				
1	24	0.14	0.08	0.02	0.00	—
2	48	0.26	0.26	0.17	0.02	—
3	88	0.26	0.29	0.29	0.10	—
4	124	0.26	0.29	0.29	0.21	—
5	224	0.21	0.29	0.29	0.26	0.03
6	324	0.22	0.29	0.29	0.29	0.04

A different effect of increasing silicate concentration in solution was observed for the silicomolybdic complex. With increasing silicate concentration the optical density of the solutions at first rises and then remains constant even with a ratio of Si:Mo considerably higher than 1:12. The data indicate that increasing concentration of silicic acid in solution does not lead to the formation of new complexes.

Apart from an examination of the conditions of formation of silicomolybdic and phosphomolybdic complexes in solution a study was also made (for the purpose of general characterization of the equilibrium) of the conditions of decomposition of the complexes under the action of reagents combined in the molybdate complex.

The experiments enabled us to obtain comparative data for the stability of the silicomolybdic and phosphomolybdic complexes. Addition of excess of phosphoric acid to the solution of the silicomolybdic complex does not lead to appreciable fall in the intensity of color of the solutions, whereas solutions of the phosphomolybdic complex are decolorized in similar experimental conditions. The obtained results demonstrate the great stability of the silicomolybdic complex in comparison with the phosphomolybdic complex.

Addition of citric acid to silicomolybdate solution does not change the color intensity; the same treatment decomposes the phosphomolybdic complex. The results of these experiments confirm the greater stability of the silicomolybdic complex in comparison with the phosphomolybdic complex.

SUMMARY

1. The equilibrium conditions in solution of phosphomolybdic and silicomolybdic complexes are considered. In solutions of the phosphomolybdic complex the processes are reversible. In solutions of the silicomolybdic complex irreversible processes are observed which are associated with the colloidal character of silicic acid.

2. The composition of colored phosphomolybdates in solution was examined by the method of physicochemical analysis. The obtained data indicate that in some conditions the formation is possible of a phosphomolybdic acid containing 24 atoms of molybdenum per atom of phosphorus. On heating to 60° only a compound with a P:Mo ratio of 1:12 is observed to be formed. For the silicomolybdic complex, in all conditions a compound with the ratio Si:Mo = 1:12 is formed.

3. The dissociation constant of the phosphomolybdic complex was determined; it was found that:

$$K_{complex} = \frac{[PO_4^{---}][(MoO_2)_2]^4}{[P(Mo_2O_{12})_4]} = 5.6 \cdot 10^{-10}.$$

4. An examination was made of the conditions of decomposition of the complexes under the influence of excess of hydrogen ions, phosphoric acid, and various complex-formers which bind molybdate. The silicomolybdic complex is characterized in all cases by a higher stability by comparison with the phosphomolybdic complex. Decomposition of the complex during standing of the solution is associated with irreversible formation of silicic acid.

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Received July 8, 1952

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• See Consultants Bureau English translation, page 957.

CRYSTALLINE ORGANOLITHIUM COMPOUNDS

ETHYLLITHIUM

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Existing methods of synthesis of organolithium compounds, with a few exceptions, yield solutions (more rarely suspensions) of the compounds. Usually the solution of the organolithium compound, containing (apart from RLi) lithium salts, alkyl halides and hydrocarbons, is brought into further reactions. A remarkably large number of diverse syntheses employing solutions of organolithium compounds has been described. The characterization (chemically or physicochemically) of organolithium compounds as such, however, necessitates isolation of the pure compound or its solution.

We were interested in the preparation of pure, crystalline ethyllithium (a most interesting compound for the study of exchange reactions with organoelement compounds) with the objective of developing methods of synthesis of pure aromatic or aliphatic-aromatic compounds of lithium.

Judging by the exchange reaction with tetraphenyllead, ethyllithium is the most active representative of the RLi series [1]:

$$C_2H_5Li > n\text{-}C_3H_7Li > n\text{-}C_4H_9Li > CH_3Li > C_6H_5C{\equiv}CLi.$$

It is also significant that ethyllithium may be recrystallized [2] or sublimed in high vacuum [3].

Up to now the synthesis of small quantities of ethyllithium, up to 0.7 g of crude material, has been performed in sealed vessels under nitrogen by the action of lithium on diethylmercury; yield up to 93% [4].

$$(C_2H_5)_2Hg + 2Li \longrightarrow 2C_2H_5Li + Hg.$$

This method could not be widely adopted owing to the very high toxicity of the initial mercury compound.

Apart from this method, the literature contains a brief reference to the possibility of synthesis of a small quantity of ethyllithium (no indication of yield) by the action of lithium on ethyl chloride followed by removal of the solvent and isolation of the pure ethyllithium by sublimation in vacuum [5].

The method of preparation which we have developed for pure, crystalline ethyllithium is based on reaction of lithium with ethyl bromide followed by its separation from the lithium bromide; for this purpose advantage is taken of the differing solubility in benzene and isopentene (or hexane)

$$C_2H_5Br + 2Li \longrightarrow C_2H_5Li + LiBr.$$

We performed the reaction of ethyl bromide with lithium in a medium of isopentene (mixture of pentenes) with b.p. 27-36°, a grey-violet, heavy precipitate was obtained which consisted of a mixture of lithium bromide and ethyllithium. On addition of benzene, the isopentene was distilled off and the ethyllithium went over in the solvent (leaving a residue of lithium bromide and excess lithium). On cooling we obtained transparent solutions of ethyllithium with an ethyllithium yield of 65%. Subsequent distillation of a portion of the benzene enabled isolation of crystalline ethyllithium (yield 30-35%). After one recrystallization from hexane we obtained pure ethyllithium. All operations in the preparation and isolation of ethyllithium must be performed in an atmosphere of pure nitrogen. It should not be forgotten that ethyllitnium inflames immediately when it comes into contact with air; flaming and carbonization of the preparation is observed even on sealing into tubes insufficiently carefully filled with nitrogen. The residues in the reaction flask after preparation of ethyllithium (lithium bromide, lithium, residues of C_2H_5Li solution) must be quickly decomposed (otherwise a fire may occur on access of air). Decomposition is effected by addition of benzene, then (carefully) of ethyl alcohol.

EXPERIMENTAL

Preparation of Crystalline Ethyllithium

a) Preparation of ethyllithium in an isopentene medium. Use was made of a 500 ml 3-necked flask connected by ground-glass fittings with a mercury seal, a reflux condenser, a dropping funnel and a nitrogen feed tube (the latter also serves for siphoning the solution) (Fig. 1). The dropping funnel, for equalizing the pressure, is connected through a three-way cock with the nitrogen tube. For purification of the nitrogen see

reference 6. A broad funnel is inserted in the vessel (through the ground-glass connection for the condenser), 200 ml isopentene is poured in and a nitrogen stream is passed. A weighed amount of lithium (3.8 g or 0.56 g-atom) is beaten into a sheet about 1 mm thick, strips 5-7 mm wide are cut from it, purified from the oxide film, and quickly cut with scissors over a funnel in a stream of nitrogen into about 90-350 pieces.

The reflux condenser (attached to a drying system*) is then connected up and the apparatus is filled with nitrogen. In the dropping funnel is placed 21.8 g ethyl bromide (0.2 mole), about 1/8 of the total volume is run in, and the stirrer is started up.

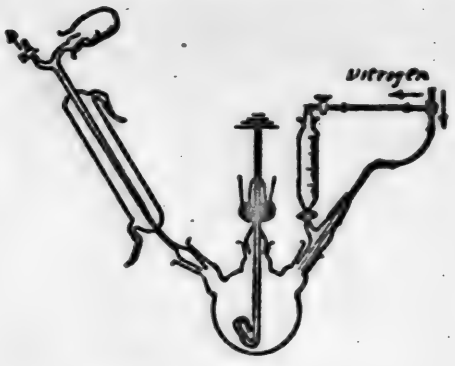

Fig. 1.

The reaction starts spontaneously after 15-20 minutes of vigorous stirring at the boiling point of isopentene (in some cases the reaction only starts after 2-2½ hours). Start of reaction is marked by spontaneous boiling, appearance of rapidly increasing turbidity, and then by a precipitate. Pieces of lithium sink to the bottom of the flask. In roughly 10 minutes after the start of the reaction the reaction mass becomes completely opaque. The color of the precipitate varies from light-grey to dark-grey; sometimes it is violet. The remainder of the ethyl bromide is added in small portions (uniformly) over a period of 3-3½ hours, after which stirring is continued with gentle boiling until bubbles cease to rise from the vicinity of the lithium particles (observation is made with heating suspended); this takes 1½-2 hours. The total duration of the reaction, starting from the addition of ethyl bromide, is 5-6 hours (in isolated instances up to 7-8 hours).

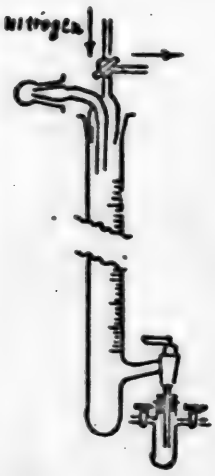

Fig. 2.

b) Preparation of benzene solution of ethyllithium. To the reaction mixture is added 100-120 ml benzene, heated to 30-35°. By turning the ground-glass connection the condenser is converted into a sloping one (Fig. 1) to which is attached a receiver (cooled with ice and water), and with continued stirring 170-180 ml isopentene is distilled off. At the conclusion of the distillation, the stirrer is stopped and a small buret (100 ml) is attached for settlement of the solution; the buret is filled with nitrogen (Fig. 2). The tap connecting the condenser to the drying system is then closed, the stirrer is lowered and, with continued heating, the solution with a considerable amount of precipitate is forced over with solvent vapors. The vessel containing the solution is disconnected and cooled at room temperature in a weak current of nitrogen. After standing for 12-14 hours there is obtained a perfectly transparent, colorless (sometimes slightly yellow) solution of ethyllithium. The volume of the solution is 90-100 ml; the concentration of the benzene solution of ethyllithium is about 1.25-1.28 N; yield of ethyllithium reaches 65%.

c) Isolation of crystalline ethyllithium. The apparatus for isolation of crystalline ethyllithium consists of a three-necked nitrogen tube (Fig. 3) of 120 ml volume, connected to a condenser and receiver and fitted with a filtration device [7]. Through the apparatus is passed about 8-10 volumes of nitrogen (in relation to the volume of the apparatus). The tap of the settling buret is joined to the nitrogen tube by means of a length of thick-walled rubber tubing; the buret is connected by a three-way cock with the nitrogen-supply system, and the transparent benzene solution of ethyllithium is run into the nitrogen tube. The upper exit is then closed (Fig. 3), a gentle stream of nitrogen is run through the condenser; and about 50-60 cc of benzene is distilled off. To the residue in the nitrogen tube is added 20 ml dry isopentene and the mixture is cooled with ice and salt. The separated crystals are removed from the sides and stirred, the lumps being crushed with a curved rod passed through the upper end of the nitrogen tube; the mass is then filtered on a porous glass filter [7], washed 3-4 times with dry pentane and dried (with passage of nitrogen and heating to 40-50°) for 30 minutes. For filtration and charging into ampoules under nitrogen, see reference 7.

* Tubes containing phosphorus pentoxide, calcium chloride and sulfuric acid.

Use is made for analysis of thin-walled ampoules into each of which is introduced about 0.04-0.05 g substance (see below respecting analysis of crystalline ethyllithium). The yield of crystalline ethyllithium is about 2.5-2.3 g or 35-33%.

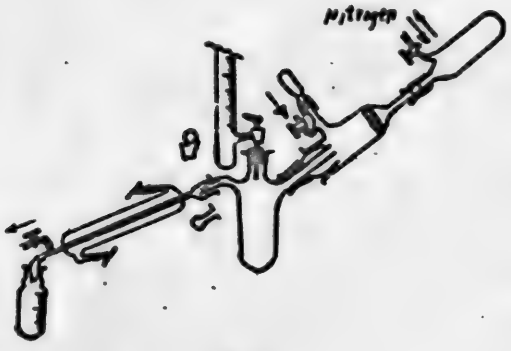

Fig. 3.

Ethyllithium is obtained in the form of a perfectly white, crystalline powder with m.p. 95° (with decomposition; determined in a capillary filled with nitrogen). The literature reports m.p. about 90° with decomposition [8].

Found %: Li 18.94, 19.00. C_2H_5Li.
Calculated %: Li 19.33.

After recrystallization from n-hexane, found %: Li 19.10, 19.16.

Ethyllithium readily dissolves in boiling benzene and hexane; on cooling it readily forms supersaturated solutions. Solubility in pentane (b.p. 28-38°): about 1 g ethyllithium is contained in 100 g solution at 18° (approximately 0.2 N solution); in isopentene (b.p. 27-35°) about 3 g ethyllithium is contained in 100 g solution at 16° and about 2 g ethyllithium at 0°; in hexane (b.p. 69°) at 55°. 100 g solution contains about 9.5 g ethyllithium, and at 18° the ethyllithium content is about 6 g; in benzene: at 16° 100 g solution contains about 7 g ethyllithium (the solution is approximately 1.66 N). The solubility in absolute ether at 18° is very high.

The yield of crystalline ethyllithium attains values of 10-20% when preparation is carried out in the same conditions in a medium of pentane.

Preparation of Ethyllithium in Ether Solution Followed by Transfer to Benzene Solution

The previously described all-glass apparatus (Fig. 1) is used. Into the flask are introduced 130 ml absolute ether and 4 g (0.57 g-atom) thinly sliced lithium (see above). The first portion of ethyl bromide is run in with stirring; vigorous boiling starts. The flask is lowered into ice water and the ethyl bromide is run in at such a speed that the vigorous boiling of the ether does not cease; this requires a period of 20 minutes. 21.8 g ethyl-bromide (0.2 mole) is introduced in all. Addition is next made of 120 ml dry benzene, the condenser is turned into the sloping position and the ether is distilled off with uninterrupted stirring. The solution is dark-grey (nearly black); with progressive distillation of the ether a white precipitate forms. The volume of distillate is about 130 ml. The warm solution is siphoned into the buret under nitrogen for the purpose of settlement (Fig.2). After about 30 minutes the solution is nearly transparent. For complete clarification it is left to stand overnight. Analysis of the solution gives an ethyllithium/lithium bromide ratio of approximately 20:3. When concentrated under nitrogen, the solution deposits a precipitate containing ethyllithium and lithium bromide in the ratio of 10:7, while the filtrate contains these substances in the approximate ratio of 7:1. It was not possible to isolate pure, crystalline ethyllithium by this method. The obtained benzene solution of ethyllithium may be utilized for further reactions.

Analysis of Organolithium Compounds

The greatest difficulty in the analysis of isolated organoalkali compounds is the weighing out of the readily oxidized and for the greater part readily inflaming compound. A dry ampoule is, therefore, first filled with nitrogen via a capillary and then closed with a piece of thickwalled elastic rubber tubing plugged with a glass rod. In the instant of weighing the sample (e.g. 0.1-0.15 g ethyllithium or 0.3-0.4 g phenyllithium) the ampoule is quickly connected (in a countercurrent of nitrogen) with an apparatus for filtration and drying of isolated organolithium compounds [9]. The tap connecting with the nitrogen supply is then closed and the ampoule is sealed. Thin-walled ampoules are used for analysis.

The sealed ampoule is placed in a thick-walled Bunsen flask (volume 500 ml) closed with a rubber stopper through which is passed a glass rod reaching to the bottom. 25-30 ml pure, dry benzene is run into the flask which is then filled with nitrogen; the ampoule is crushed by a swift movement. Ethyllithium goes into solution (phenyl-lithium becomes wetted with benzene). With the stopper slightly loosened, addition is made of 5 ml absolute alcohol and the mixture is shaken before adding 50-100 ml water. Titration is performed with 0.1 N sulfuric acid using phenolphthalein. Nitrogen is passed through the side tube of the flask during the analysis.

For the analysis of ethyllitnium solutions it proved convenient to employ small conical flasks provided with two taps for passage of nitrogen (Fig. 4). Into 3-4 small flasks was first introduced a small quantity of benzene (otherwise the introduction of the ethyllithium solution would result in violent sputtering against the walls), the flasks were stoppered, linked together in series, and a dry nitrogen stream passed through for 10-15 minutes. After that, samples of 1-2 ml were quickly run in from the settling buret (Fig. 2) and decomposed and titrated in the usual manner [6,10].

Fig. 4.

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Received July 25, 1952.

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* See Consultants Bureau translation.

CHARACTERIZATION OF PHTHALIMIDINEACETIC ACID

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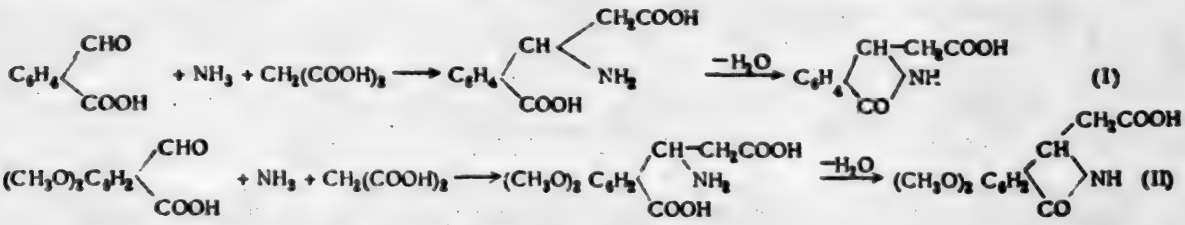
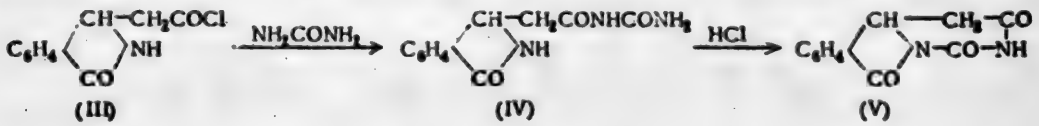
The method developed in our laboratory for the preparation of β-amino acids [1] was extended in 1930 to the synthesis of dimethoxyphthalimidineacetic acid [2] and in 1944 to that of phthalimidineacetic acid [5]. In these investigations it was shown that reaction of aromatic o-aldehyde acids with malonic acid in presence of alcoholic ammonia yields chiefly phthalimidineacetic acid (I) or its corresponding dimethoxy derivative (II)



In our investigation we have attempted a more detailed study of the properties of phthalimidineacetic acid (I). With this objective we prepared its ethyl ester amide and ureide, and carried out experiments on the preparation of the corresponding complex dihydrouracil from the ureide of the acid according to the scheme:

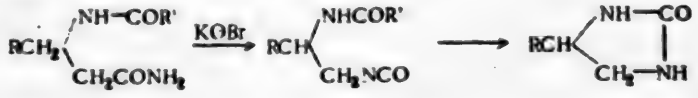


(III) (IV) (V)

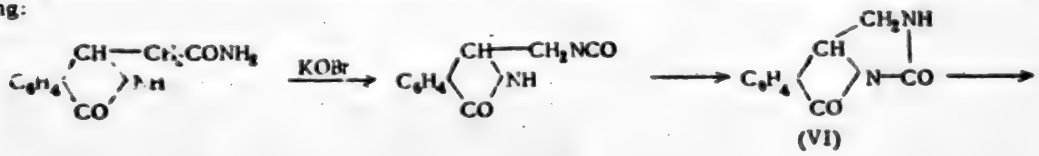
In studying these reactions it was found that the chloride of phthalimidineacetic acid, readily prepared in good yield (96%), condenses with urea to form the corresponding ureide (IV). This compound, however, does not undergo ring closure, and the complex tricyclic system (V) could not be obtained. In all the experiments either the ureide was recovered unchanged or the original phthalimidineacetic acid (I) was formed.

Attempts to obtain the ureide of phthalimidineacetic acid by the action of urea on the ethyl ester of the acid in presence of sodium ethylate led to the isolation of a mixture of amide and ureide, and no ring closure was detected.

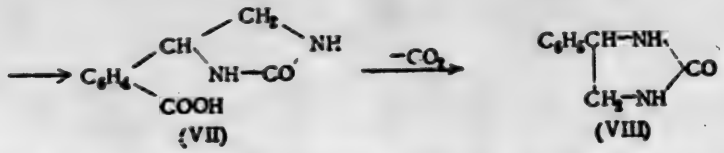
For the purpose of further characterization of phthalimidineacetic acid, a study was made of the reaction of the acid amide with KOBr in the conditions of the Hofmann reaction. Similar investigations with β-amino acid amides were frequently carried out successfully by Kanevskaya [4] and in our laboratory [5], and in all cases it was established that the main reaction product is the corresponding imidazolone derivative formed via the isocyanate



In the case here studied, it transpired that the reaction proceeds in a somewhat more complicated manner: in place of the anticipated anhydride of phenylimidazolone carboxylic acid (VI), which is also a tricyclic system, there is obtained the phenylcarboxy derivative of the imidazolone (VII), apparently due to rupture of the lactam ring:



(VI)



(VII) (VIII)

The structure of the phenylimidazolone carboxylic acid was established by a study of its properties, by the elementary analysis, and by the result of decarboxylation. The latter reaction proceeds either through simple repeated fusion of the compound, or, better, by heating a mixture of the phenylimidazolone carboxylic acid and naphthalene at 200-220°. The resultant product (VIII) was identical in all respects with the phenylimidazolone prepared by Kanevskaya [4] and Kiseleva [5].

EXPERIMENTAL

Phthalimidineacetyl chloride. Gradual addition is made to 11.5 g phthalimidineacetic acid, with constant stirring, of 28.7 g thionyl chloride, and the solution is heated for about an hour on a water bath at 30-35° and toward the end at 40°. Gradual precipitation occurs of snow-white, small rhombic crystals. Complete precipitation is ensured by standing the reaction mixture for 3 hours; the crystals are then drained and washed with dry ether. Yield 12.77 g. The chloride melts at 123-124° (with decomp.); it is sparingly soluble in ether, benzene and xylene, readily soluble in acetic anhydride.

Found %: N 6.96, 6.97; Cl 16.35, 16.20. $C_{10}H_8O_2NCl$. Calculated %: N 6.68; Cl 16.94.

Phthalimidineacetic acid ureide. 2 g freshly prepared phthalimidineacetyl chloride is mixed with 1.8 g urea, put into 25 ml dry benzene and the mixture heated for 6 hours in a flask under a reflux condenser on a water bath. The precipitate is filtered, washed with ether and then with ammonia solution. Yield of unpurified product 2.14 g or about 96.4% of theory, calculated on the acid chloride. M.p. 222-223° (with decomp.). After one recrystallization from alcohol the m.p. rises to 229-230° (with decomp.). The product separates from alcohol as small, white, transparent prisms. Sparingly soluble in water, ethyl alcohol and dilute hydrochloric acid.

The preparation proved to be inactive in pharmacological tests.

Heating of the ureide with a large excess of conc. hydrochloric acid (sp. gr. 1.19) does not result in ring closure but only in hydrolysis of the ureide, and phthalimidineacetic acid is formed (m.p. 180-181°).

N-Acetylphthalimidineacetic acid. 1 g phthalimidineacetic acid is mixed with a large amount of acetic anhydride (25-30 g) and boiled for 4 hours. After cooling, the mass is diluted with double the amount of water. The 0.67 g of precipitate is recrystallized from alcohol to give long, transparent, small prisms, m.p. 186-188°.

Found %: N 6.05, 6.21. $C_{12}H_{11}O_4N$. Calculated %: N 6.00.

The ethyl ester. 2.75 g phthalimidineacetic acid and 7 g dry ethyl alcohol, saturated with hydrogen chloride, are heated for 4 hours on the water bath; the excess alcohol is then distilled off; to the residue is added triple the amount of water. The separated viscous, yellow-brown oil gradually solidifies. It is neutralized with sodium carbonate solution and the resultant white flocs are filtered off and washed with water. Yield of crude product 2.6 g or about 82.5% of theory, calculated on phthalimidineacetic acid. M.p. 115-116°, rising to 119-120° after recrystallization from ether (white, transparent platelets). Readily soluble in alcohol, poorly in water.

Found %: N 6.58, 6.62. $C_{12}H_{13}O_3N$. Calculated %: N 6.39.

Reaction of ethyl phthalimidineacetate with urea. 2 g of the ester and 0.6 g urea are heated for 3 hours in an alcoholic solution of sodium ethylate (0.23 g in 5 ml alcohol) on a water bath at 70°. 0.98 g substance with m.p. 215-218° was separated. After recrystallization from water the m.p. rose to 220-221°. The compound proved to be the amide of phthalimidineacetic acid and did not depress the melting point of a specially prepared sample (see below). In addition 0.3 g of a compound less easily soluble in water was isolated. When recrystallized from a large quantity of water, the ureide of phthalimidineacetic acid with m.p. 229-230° was isolated; it did not depress the m.p. of the ureide from another batch.

More prolonged heating of the ester with urea in an alcoholic solution of sodium ethylate (3 hours on the boiling water bath) yielded exclusively the amide of phthalimidineacetic acid.

Phthalimidineacetamide. A dry ammonia stream is passed into a mixture of 2 g phthalimidineacetyl chloride and 25 ml dry benzene for 3 hours with constant cooling with ice water. The precipitate is filtered after standing for 8-10 hours and washed with sodium carbonate solution and water. After drying, 1.46 g product with m.p. 217-218° is obtained in the form of needlets. After recrystallization from water the m.p. rose to 224-225°. Yield 1.05 g or 58% calculated on the chloride.

Found %: N 14.90, 14.83. $C_{10}H_{10}O_2N_2$. Calculated %: N 14.74.

The highest yield of the amide is obtained by passing dry ammonia into a mixture of the acid chloride, dry toluene and xylene. In the same conditions as described above, 12 g acid chloride gave 7.8 g amide or about 71% of theory.

Methylamide of phthalimidineacetic acid. Prepared by reaction of the acid chloride with methylamine; melts at 183-185°; crystallizes in slender, white needlets; soluble in acids, alcohol and hot water; insoluble in caustic alkalies and ether.

Found %: N 13.82. $C_{11}H_{12}O_2N_2$. Calculated %: N 13.72.

2'-Carboxyphenyl-5-imidazolone (VII). Gradual addition is made at −5° to −7° of 5 g phthalimidineacetamide to a solution of 8.4 g bromine and 18.22 g potassium hydroxide in 90 ml water. The greater part of the amide dissolves. After the whole amount has been introduced, the reaction mass is heated for 30-40 minutes at 75-80°; it is then cooled externally with ice water and acidified with strong hydrochloric acid. A yellow precipitate (5.3 g) comes down; it is worked up with 10% sodium carbonate and filtered from the small quantity of residue insoluble in the soda. Acidification of the resultant alkaline solution with hydrochloric acid brings down 3.02 g of a mixture of two substances with the unsharp m.p. of 168-185°. Microscopic observation reveals transparent white platelets and clusters of needlets.

Two treatments with absolute alcohol and recrystallization from water of the alcohol-insoluble residue gave 0.6 g of a compound with m.p. 229-230° and the elementary composition $C_{10}H_{10}O_3N_2$.

On the basis of analyses and a study of the properties of this substance, the structure of carboxyphenylimidazolone could be assigned to it.

Found %: C 58.29, 58.13; H 4.37, 4.97; N 13.61, 13.62. $C_{10}H_{10}O_3N_2$. Calculated %: C 58.25; H 4.85; N 13.59. Determination of the acid equivalent: found 205.3; calculated 206.

During the melting point determination the substance melted at 229-230° with decomposition and vigorous gas evolution. The substance solidifying in the capillary melts at 161-162° when heated again. This melting point is characteristic of 5-phenylimidazolone (VIII). Consequently the substance undergoes decarboxylation when heated.

Decarboxylation can be most simply effected by heating with naphthalene. 0.18 g carboxy derivative is mixed with 10 times the amount of naphthalene and the mixture heated at the boiling point of naphthalene for 1½-2 hours. After cooling, the pulverized mass is treated 3 times with hydrochloric acid solution (1:1). The combined acid solutions are made alkaline with 15% sodium hydroxide solution and left to stand for 1½-2 hours while cooling externally with ice water. The precipitate is drained at the pump. After drying, the yield is 0.07 g. The product melts sharply at 160-161° after recrystallization from water and alcohol and does not depress the melting point of an authentic specimen of pure phenylimidazolone.

It was previously pointed out that 3.02 g of the mixture of substances separated from sodium carbonate solution was worked up with alcohol. The alcohol-soluble compound was isolated in the amount of 2.05 g and identified as phthalimidineacetic acid.

After removal of the carboxyphenylimidazolone, the acid filtrates contain mainly phthalimidineacetic acid which was isolated from the filtrates both as such and as the ethyl ester; for this purpose the filtrates were made alkaline with ammonia, evaporated to dryness and treated with absolute alcohol.

The Hofmann reaction was repeated several times with slight variations of temperature, alkali concentration and duration of reaction with alkali hypobromite. The yields of carboxyphenylimidazolone fluctuated fairly widely (13% when the amide was heated immediately after introducing it into hypobromite solution; 26% if the introduced amide was heated only after standing for 3 hours at room temperature).

In all cases two main products were isolated: carboxyphenylimidazolone and phthalimidineacetic acid.

SUMMARY

1. Phthalimidineacetic acid was characterized through the preparation of its acid chloride, ureide, amide, methylamide, ethyl ester and N-acetyl derivative.

2. A study was made of the condensation of the ethyl ester of phthalimidineacetic acid with urea in presence of sodium ethylate, and it was established that the reaction yielded the amide or a mixture of the ureide and the amide of phthalimidineacetic acid.

3. It was established that reaction of the amide of phthalimidineacetic acid with potassium hypobromite gives 2'-carboxyphenyl-6-imidazolone, which readily decarboxylates to the previously known 5-phenylimidazolone.

4. It is shown that the yield of carboxyphenylimidazolone depends in the main on the duration of the reaction of the amide with potassium hypobromite.

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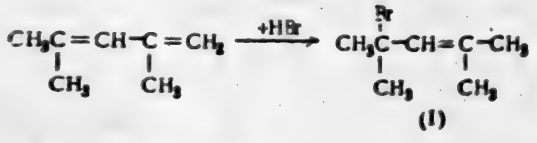
Received July 22, 1952.

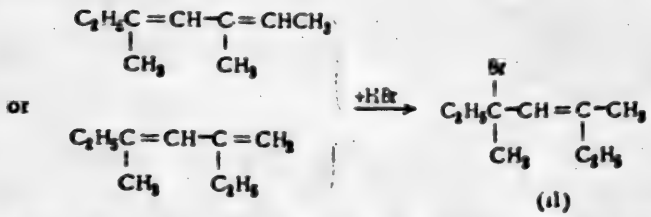
XXXVIII. SYNTHESIS OF ALKENES AND ALKANES WITH TWO QUATERNARY CARBON ATOMS

R. Ya. Levina, N. P. Shusherina, N. I. Volchinskaya and M. Yu. Lurye

Addition of hydrogen bromide to some conjugated alkadienes with an iso structure, for example to 2,4-dimethylpentadiene-1,3 and 3,5-dimethylheptadiene-2,4, leads to formation of tertiary bromides of the allyl type whose structure in each case excludes the possibility of formation of the isomeric bromide by allyl rearrangement:

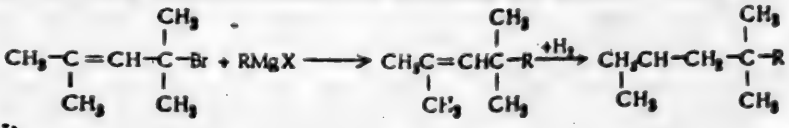


(I)

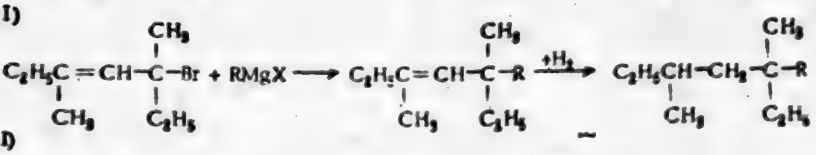


(II)

In our previous researches [1,2,3] it was established that the reaction between allylic bromides and primary or secondary alkyl magnesium halides is a method of synthesis of olefinic hydrocarbons, hydrogenation of which could yield paraffinic hydrocarbons containing one quaternary carbon atom:



(I)

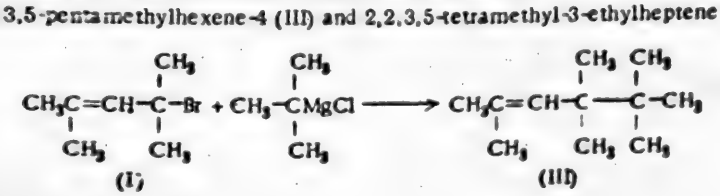


(II)

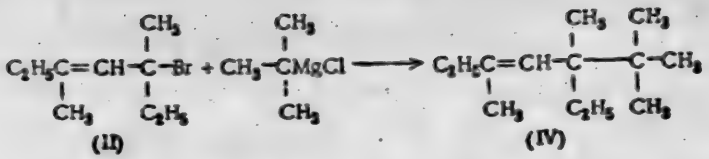
where R = CH_3, C_2H_5, C_3H_7, C_4H_9, iso-C_3H_7, iso-C_4H_9 and iso-C_5H_{11}

The structure of the so-synthesized hydrocarbons was confirmed by the methods of oxidation or ozonization and Raman spectrography [1,3].

In the present investigation, these tertiary allylic bromides (I and II) (2,4-dimethylpentadiene-1,3 hydrobromide and 3,5-dimethylheptadiene-2,4 hydrobromide) were brought into reaction with an organomagnesium compound containing a tertiary alkyl group (tert-butyl magnesium chloride), this reaction served as a method of synthesis of difficultly accessible branched olefinic hydrocarbons containing two quaternary carbon atoms: 2,2,3,3,5-pentamethylhexene-4 (III) and 2,2,3,5-tetramethyl-3-ethylheptene-4 (IV)



(I) (III)



(II) (IV)

Catalytic hydrogenation of the synthesized alkenes yielded the corresponding alkanes: 2,2,3,3,5-pentamethylhexane and 2,2,3,5-tetramethyl-3-ethylheptane.

EXPERIMENTAL

2,2,3,3,5-Pentamethylhexene-4 and 2,2,3,3,5-pentamethylhexane. Tert-butyl chloride was prepared by addition of hydrogen chloride to isobutene in the gas phase [4].

An ethereal solution (1:1) of 70 g (0.75 mole) tert-butyl chloride was slowly added with heating (at the rate of not more than one drop per second) to 18 g magnesium covered with a layer of absolute ether and previously activated with 1.5 ml ethylene bromide. After introduction of the total amount of tertiary chloride, the reaction mixture was heated with stirring for two hours. To the so-obtained ethereal solution of tert-butyl magnesium chloride, cooled to −40°, was added dropwise over a period of 30-40 minutes an ethereal solution (1:1) of the freshly prepared hydrobromide of 2,4-dimethylpentadiene-1,3* (72 g, 0.5 mole), also cooled to −30°. The reaction mixture was then stirred for 3 hours while being cooled to −30° and for 2 hours at room temperature, allowed to stand overnight, and heated on the following day for 8 hours with continuous stirring. Decomposition was effected by pouring the reaction mixture on to ice containing ammonium chloride. The ether extract was washed and dried with calcium chloride, the ether was distilled off and the residue heated over sodium (6 hours); the obtained hydrocarbon was distilled off from higher boiling fractions and then redistilled over sodium in a column with 40 theoretical plates. The isolated 2,2,3,3,5-pentamethylhexene-4 (yield 17% of the theoretical) possessed the following constants: b.p. 170-170.2° (760 mm); n_D^{20} 1.4470; d_4^{20} 0.7836; MR_D 52.60. $C_{11}H_{22}$. Calculated: MR_D 52.53.

7.530 mg substance: 23.660 mg CO_2; 9.590 mg H_2O. 6.310 mg substance: 19.850 mg CO_2; 8.030 mg H_2O. Found %: C 85.75, 85.85. H 14.25, 14.24. $C_{11}H_{22}$. Calculated %: C 85.60; H 14.40.

2,2,3,3,5-Pentamethylhexene-4 has not been described in the literature.

Fractionation of the higher boiling fraction gave the dimer of 2,4-dimethylpentadiene-1,3 with b.p. 217-218° at 760 mm (yield 17% calculated on the initial hydrobromide). The formation of 2,4-dimethylpentadiene-1,3 is explained by cleavage of hydrogen bromide from the tertiary hydrobromide under the action of the organomagnesium compound.

Catalytic hydrogenation of 2,2,3,3,5-pentamethylhexene-4 was carried out over nickel-on-alumina at 160-170° and led to formation of 2,2,3,3,5-pentamethylhexane which had the following constants (after redistillation in a column (over sodium):

B.p. 172.8-173.5 (760 mm); n_D^{20} 1.4302; d_4^{20} 0.7673; MR_D 52.68; calculated 52.99.

2,2,3,3,5-Pentamethylhexane has not been described in the literature.

2,2,3,5-Tetramethyl-3-ethylpentene-4 and 2,2,3,5-tetramethyl-3-ethylheptane. The preparation of the hydrobromide of 3,5-dimethylheptadiene-2,4** and its reaction with tert-butyl magnesium chloride was carried out by the above-described procedure (for the hydrobromide of 2,4-dimethylpentadiene-1,3). After working up the reaction product in the usual manner and distilling off the ether, the residue was fractionally distilled over sodium. Two fractions were obtained:

* The hydrobromide of 2,4-dimethylpentadiene-1,3 [2] was prepared by passing dry hydrogen bromide into the cooled dienic hydrocarbon (b.p. 93-94° at 755 mm; n_D^{20} 1.4448; d_4^{20} 0.7376) until the weight increase corresponded to that required for the addition of one molecule of HBr. The hydrobromide was not distilled, but directly after preparation it was dissolved in an equal volume of absolute ether and brought into reaction with the tert-butyl magnesium chloride.

** Hydrogenation was performed on a mixture of diene hydrocarbons —3,5-dimethylheptadiene-2,4 and 4-methyl-2-ethylhexadiene-1,3— whose components differed only in the position of the double bond: b.p. 136-142° (760 mm); n_D^{20} 1.4495; d_4^{20} 0.7675 [3].

1) b.p. 130-136°; n_D^{20} 1.4260; 2) b.p. 200-211°.

Distillation of the second fraction in a column with 40 theoretical plates gave a 14% yield of 2,2,3,5-tetramethyl-3-ethylheptene-4:

B.p. 210.5-211.5° (755 mm); n_D^{20} 1.4574; d_4^{20} 0.8032; MR_D 61.91. $C_{13}H_{26}F$. Calculated: MR_D 61.76.

5.792 mg substance: 18.150 mg CO_2; 7.490 mg H_2O. 6.340 mg substance: 19.905 mg CO_2; 8.220 mg H_2O. Found %: C 85.52, 85.68; H 14.47, 14.51. $C_{13}H_{26}$. Calculated %: C 85.72; H 14.28.

2,2,3,5-Tetramethyl-3-ethylpentene-4 is not described in the literature.

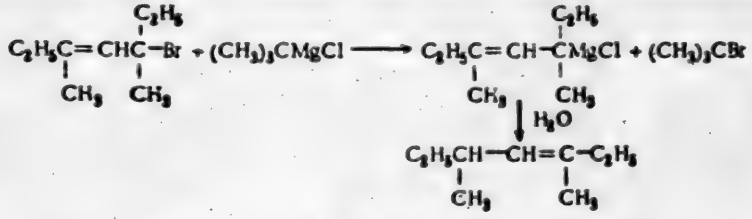
Distillation of the lower boiling fraction (b.p. 130-136°) in a column with 40 theoretical plates gave a hydrocarbon (yield 55% of the theoretical calculated on the initial hydrobromide) with the following constants:

B.p. 130.5-131° (750 mm); n_D^{20} 1.4222; d_4^{20} 0.7353; MR_D 43.54. $C_9H_{18}F$. Calculated: MR_D 43.29.

The constants indicate that the hydrocarbon is 3,5-dimethylheptene-3.

Literature data for 3,5-dimethylheptene-3 [5]: b.p. 130.5-130.6° (749 mm); n_D^{20} 1.4218; d_4^{20} 0.7350.

The formation of 3,5-dimethylheptene-3 by reaction of tert-butyl magnesium chloride with the hydrobromide of 3,5-dimethylheptadiene-2,4 may be explained by the following secondary reaction:



Catalytic hydrogenation of 2,2,3,5-tetramethyl-3-ethylheptene-4 over nickel-on-alumina at 160-170° led to formation of 2,2,3,5-tetramethyl-3-ethylheptane with the following constants (after distillation in a column): b.p. 214.5-215° (760 mm); n_D^{20} 1.4440; d_4^{20} 0.7891; MR_D 61.83. calculated 62.23.

5.740 mg substance. 17.780 mg CO_2, 7.890 mg H_2O. 7.130 mg substance: 22.140 mg CO_2; 9.710 mg H_2O. Found %: C 84.53, 84.73, H 15.38, 15.24. $C_{13}H_{28}$. Calculated %: C 84.80, H 15.28.

A Raman spectrographic study of the prepared alkane revealed frequencies, according to the data of Stepanov [6], characteristic of hydrocarbons possessing two quaternary carbon atoms.

SUMMARY

1. Our previously developed method of synthesis of hydrocarbons containing a quaternary carbon atom was applied to the reaction of the hydrobromides of 2,4 dimethylpentadiene-1,3 and 3,5-dimethylheptadiene-2,4 with organomagnesium compounds to give previously undescribed hydrocarbons with two quaternary carbon atoms —2,2,3,3,5-pentamethylhexene-4 and 2,2,3,5-tetramethyl-3-etnylheptene-4.

2. Hydrogenation of these hydrocarbons yielded the difficultly accessible alkanes, 2,2,3,3,5-pentamethylhexane and 2,2,3,5-tetramethyl-3-ethylheptane, not previously described in the literature.

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[2] R. Ya. Levina, A. A. Fainzilberg and N. P. Shusherina, J. Gen. Chem., 18, 1775 (1948).

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[4] R. Ya. Levina, V. R. Skvarchenko and N. I. Volchinskaya, Bull. Moscow State Univ., No. 12, 77 (1951).

[5] R. Ya. Levina, N. P. Shusherina and E. G. Treshchova, Bull. Moscow State Univ., No. 2, 107 (1952).

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Received November 14, 1952

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*. See Consultants Bureau translation, p. 903.

** See Consultants Bureau translation, p. 641.

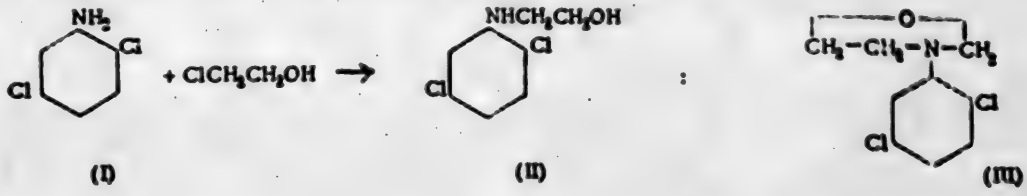
THE PROBLEM OF THE REACTION OF α-HALOHYDRINS WITH AMINES

F. F. Petrov and E. S. Lagucheva

Krasusky [1] stated that "the formation of α-amino alcohols from α-monochlorohydrins proceeds through α-oxides" which are intermediate products in the course of reaction of ammonia and amines with α-monochlorohydrins.

As we know, the foregoing observation of Krasusky and his rule for the order of addition of ammonia and amines to asymmetrical oxides is utilized for determination of the structure of amino alcohols prepared by reaction of α-halohydrins with ammonia and amines. But Krasusky also suggested the possibility of direct substitution of the halo compound at an amino group in the reactions of α-halohydrins with amines. However, he did not produce an example of this.

In this connection it appeared of interest to consider the reaction of ethylene chlorohydrin with 2,5-dichlorophenylamine (I). This reaction proceeds smoothly with heating in presence of water (procedure of Shorygin [2,3]), with formation for the most part of 2,5-dichlorophenylethanolamine (II) (2,5-dichlorophenyl-β-hydroxyethyl amine). But, as was found, in the same conditions the corresponding chlorohydrin of ethylene oxide does not react with 2,5-dichlorophenylamine. It is clear from this that the reaction of ethylene chlorohydrin with 2,5-dichlorophenylamine does not proceed according to Krasusky's rule, i.e., not through the stage of formation of ethylene oxide followed by the latter's reaction with the amine, but involves direct substitution of the chlorohydrin at the amino group. This is clearly represented by the following scheme:



(I) (II) (III)

Formation of 2,5-dichlorophenylethanolamine is confirmed by analysis for the nitrogen content and by transformation into N-(2,5-dichlorophenyl)-oxazolidine (III)

EXPERIMENTAL

2,5-Dichlorophenylethanolamine (2,5-dichlorophenyl-β-hydroxyethylamine) was prepared by reaction of 486 g (3 moles) of 2,5-dichlorophenylamine with 362.2 g (4.5 moles) ethylene chlorohydrin in presence of 43.5 ml water. The reaction was performed in a three-necked flask fitted with reflux condenser for a period of 19 hours with uninterrupted mechanical stirring. During the reaction the temperature was held within the range of 130-135°. At the end of the reaction the water and excess ethylene chlorohydrin were distilled off in the vacuum of a water jet pump. The residue was neutralized with saturated soda solution (159 g Na_2CO_3). The product was extracted with ether, separated from the water layer, dried with potassium carbonate, filtered, and fractionated. Ether was first distilled off on the water bath, and then the product was fractionated in vacuum. The first fraction was unreacted 2,5-dichlorodiphenylamine (128 g came over up to 130° at 3 mm). The next fraction was 41 g at 130-163° (3 mm). Then the 2,5-dichlorophenylethanolamine (256 g) came over at 163-165° (3 mm). The viscous still residue weighed 73 g.

2,5-Dichlorophenylethanolamine solidified in the receiver to a dense crystalline white mass contaminated by a yellowish oil. Its yield was 56.20%, calculated on the reacted 2,5-dichlorophenylamine. The 2,5-dichlorophenylethanolamine was purified by recrystallization from aqueous alcohol, from which it came down as white needles with m.p. 53-54°.

1.2310 g substance: 11.10 ml 0.5 N H_2SO_4. 1.1063 g substance: 10.00 ml 0.5 N H_2SO_4. Found %: N 6.32, 6.33. $C_8H_9ONCl_2$. Calculated %: N 6.79.

We also attempted to prepare 2,5-dichlorophenylethanolamine by passing ethylene oxide into 2,5-dichlorophenylamine heated to 100-150°, but this method failed. This reaction is not catalyzed by water, alcohol or hydrochloric acid taken in small quantity.

N-(2,5-Dichlorophenyl)-oxazolidine. Into a flask fitted with a stirrer and reflux condenser was introduced 41.2 g (0.2 mole) 2,5-dichlorophenylethanolamine dissolved in 30 ml alcohol. To the solution was gradually added from a dropping funnel 32.4 g 37% formaldehyde (0.4 mole CH_2O). The reaction was conducted with constant stirring and was accompanied by evolution of heat. After the whole amount of formaldehyde had been added, the stirring of the reaction mass was continued for a further 30 minutes. At the conclusion of the reaction the alcohol was distilled off from the reaction product in a low vacuum. The N-(2,5-dichlorophenyl)oxazolidine was then separated from the aqueous layer and subjected to vacuum fractionation. The N-(2,5-dichlorophenyl)-oxazolidine fraction was collected at 137-139° (4 mm). Yield 28.03 g (64.30% of the theoretical). The distilled product was a light-yellow oil.

d_{20}^{20} 1.3709; n_D^{20} 1.5956; MR_D 54.08; calculated 53.36.

0.9045 g substance: 40.2 ml 0.1 N H_2SO_4. 1.5848 g substance: 69.0 ml 0.1 N H_2SO_4. Found %: N 6.21, 6.09. $C_9H_9ONCl_2$. Calculated %: N 6.42.

SUMMARY

1. It was established that the formation of 2,5-dichlorophenylethanolamine from ethylene chlorohydrin and 2,5-dichlorophenylamine does not proceed according to Krasutsky's mechanism, i.e., through the stage of formation of ethylene oxide and reaction of the latter with the amine, but through direct substitution of the halo compound at the amino group.

2. The conversion of 2,5-dichlorophenylethanolamine into N-(2,5-dichlorophenyl)-oxazolidine is described.

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Received October 10, 1952

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REACTION OF PIPERYLENE AND 2,4-HEXADIENE WITH UNSATURATED NITRO COMPOUNDS

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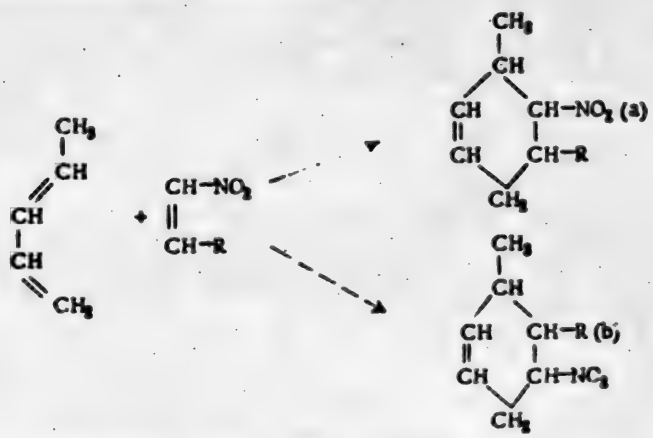
In continuation of the study of the reactions of the diene synthesis with piperylene and 2,4-hexadiene undertaken some years ago [1,2], we have condensed piperylene with nitroamylene, nitrostyrene, and furylnitroethylene, and 2,4-hexadiene with nitrostyrene and furylnitroethylene. The possibility of utilizing α,β-unsaturated nitro compounds in the diene synthesis with acyclic dienes had been demonstrated as far back as 1938 in the reactions of butadiene, isoprene and 2,3-dimethylbutadiene with nitroamylene and nitrostyrene [3-5]. Up to now, however, the question of orientation in the reactions of nitrodienophiles with unsymmetrical dienes has not been discussed in the literature. We considered it to be a matter of interest to fill this gap by a detailed examination of the reaction of nitroamylene and nitrostyrene with piperylene and on the basis of the evidence of the structure of the resultant adducts to show the order of addition. A further objective of the study of the reactions of nitrostyrene and furylnitroethylene (application of the latter as a dienophile is here described for the first time) with piperylene, hexadiene and butadiene (the latter condensed with furylnitroethylene) was the widening of the field of synthesis of hydroaromatic nitro compounds with the help of the diene reaction.

The formation of two isomeric adducts may be expected to result from reaction of nitrostyrene, nitroamylene and furylnitroethylene with piperylene:



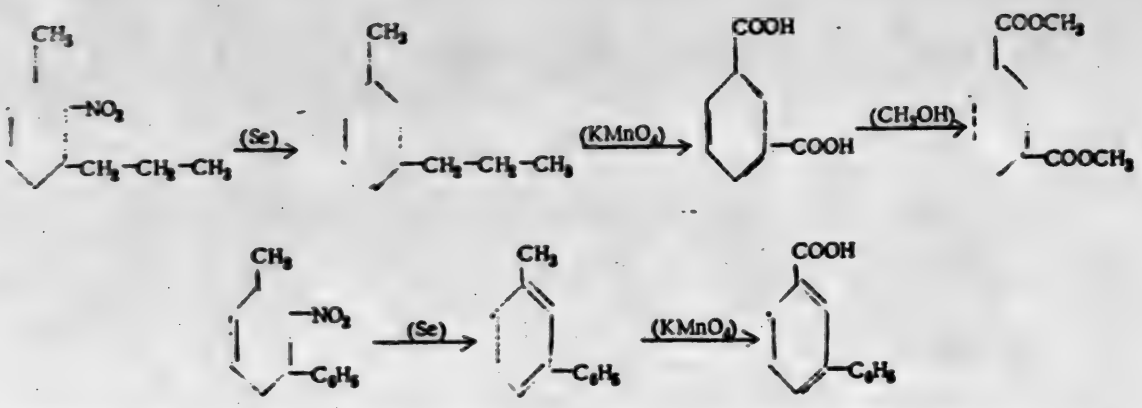
where R = $-CH_3$, $-CH_2-CH_3$, $-C_6H_5$, $-\underset{\underset{O}{\|}}{C}-H$

On the basis, however, of electronic considerations which indicated possible polarization of our selected reactants (considerations expounded in one of our earlier communications [1]), we were inclined to expect the formation of only adduct (a). Experiment actually confirmed our ideas.

Heating of piperylene with nitroamylene, nitrostyrene and furylnitroethylene in sealed tubes without a solvent at 150° for 8-15 hours gave, respectively, 2-methyl-6-n-propyl-1-nitro-Δ^3-cyclohexene, 2-methyl-6-phenyl-1-nitro-Δ^3-cyclohexene, and 2-methyl-6-α-furyl-1-nitro-Δ^3-cyclohexene.

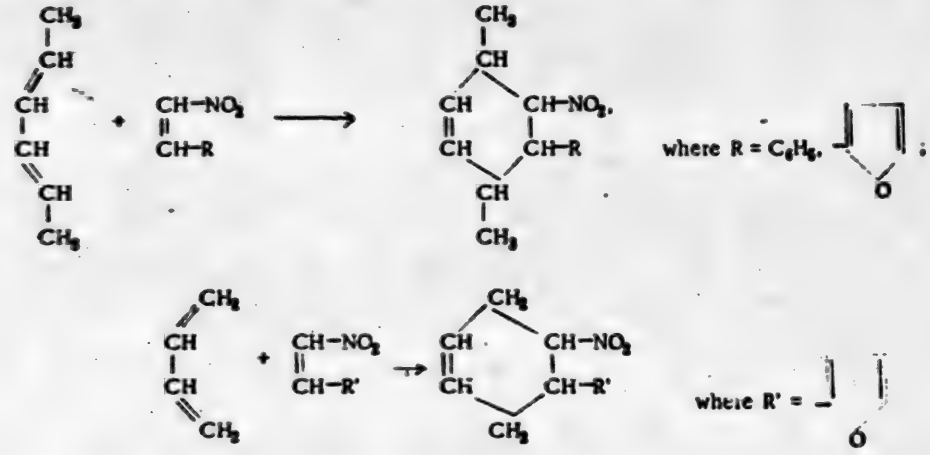
Evidence for the structure of the adducts was obtained by selenium dehydrogenation at 320-350° for 20 hours followed by oxidation of the dehydrogenation products to aromatic acids in accordance with the schemes:*

* The structure of the piperylene-furylnitroethylene adduct, due to its high resinifying tendency, was not demonstrated but was inferred by analogy with the other adducts.



When the adducts are heated with selenium at a temperature at which dehydrogenation does not yet take place (270-280°), evolution of oxides of nitrogen and water was observed, which is consistent with our previous observations [1] that functional groups of the type of CN, CHO, COOH and COOR, attached to a hydroaromatic ring, are eliminated in course of dehydrogenation.

In similar conditions the diene synthesis of 2,4-hexadiene with nitrostyrene and furylnitroethylene was performed, and also that of furylnitroethylene with butadiene:



In view of the fact that in the specified conditions the formation is possible of only one type of adduct, their structure was not considered.

All the synthesized hydroaromatic nitro compounds (with exception of the adduct of piperylene with nitrostyrene, m.p. 80-82°) are oily liquids which seriously irritate the mucous membranes of the nose and eyes.

In the case of adducts of piperylene hexadiene and with nitrostyrene, the possibility was examined of their reduction to the corresponding amines with the help of iron filings in an acetic acid medium. 2-Methyl-6-phenyl-Δ^3-cyclohexenylamine (m.p. of hydrochloride 268-270°) and 2,5-dimethyl-6-phenyl-Δ^3-cyclohexenylamine (m.p. of hydrochloride 290-292°) were prepared and characterized in the form of their hydrochlorides.

The constants of the prepared compounds are listed in the table.

EXPERIMENTAL

1. 2-Methyl-6-n-propyl-1-nitro-Δ^3-cyclohexene (I). 7 g (0.06 mole) of 1-nitroamylene-1 [8], 7.2 g (0.18 mole) of piperylene, and 0.1 g of hydroquinone were heated in sealed tubes for 15 hours at 150°. After distilling off the excess of diene, the residue was vacuum-fractionated from an Arbuzov flask to give 11 g of (I) (70%) in the form of a yellow oil with a strong odor which irritated the mucous membranes.

B.p. 108-110° at 6 mm; d_4^{20} 1.0030; n_D^{20} 1.4728; MR_D 51.19; calculated 51.40.

0.0922 g substance: 6.4 ml N_2 (22°, 753 mm). Found %: N 7.90. $C_{10}H_{17}O_2N$. Calculated %: N 7.65.

Determination of the structure of (I). 2 g of (I) was heated with 10 g selenium black in a sealed tube for 6-7 hours at 280°. When the tube was opened the odor of nitrogen oxides was detected and water droplets had condensed on the sides. The tube was again sealed and heated for another 20 hours at 320-350°. The tube was opened (H_2Se was evolved), the contents extracted with ether, the ether solution filtered, and the residue distilled in vacuum from an Arbuzov flask. The condensate was an oily liquid with b.p. 78-80° at 10 mm; n_D^{20} 1.5030 (close to the constants of m-propyltoluene: b.p. 181.5-182.5°; n_D^{20} 1.4951 [9]); it was oxidized with aqueous potassium permanganate solution with heating on the water bath and vigorous shaking for 20 hours. At the end of the oxidation the manganese dioxide was repeatedly washed with boiling water, the wash liquors were combined with the main filtrate and the whole evaporated on the water bath to a small volume. After acidification with dilute hydrochloric acid (1:2) the white precipitate was recrystallized from water. The m.p. of the substance and of a mixed specimen with isophthalic acid was 345-347°. The prepared acid was esterified to the dimethyl ester (using CH_3OH + HCl). The m.p. of the ester and that of its mixture with dimethyl-m-phthalate was 67-68° (recrystallized from dilute alcohol) [6].

2. 2-Methyl-6-phenyl-1-nitro-Δ^3-cyclohexene (II). 5 g (0.03 mole) β-nitrostyrene [10], 7 g (0.09 mole) piperylene and 0.1 g hydroquinone were heated in sealed tubes for 15 hours at 150°. After opening the tubes and distilling off the excess of piperylene, the residue solidified. Recrystallization from alcohol gave 6 g (87%) of (II) in the form of long, white needles, m.p. 80-82°.

0.1735 g substance: 9.7 ml N_2 (19.5°, 758 mm). Found %: N 6.41. $C_{13}H_{15}O_2N$. Calculated %: N 6.51.

Evidence of structure of (II). 2 g of (II) was heated with a fivefold excess of selenium in a sealed tube for 20 hours at 320-350°. At the conclusion of dehydrogenation the contents of the tube were extracted with ether, the solution filtered, the ether driven off and the residue fractionated in vacuum from an Arbuzov flask. The distillate was a viscous oil with b.p. 147-150° at 20 mm, n_D^{20} 1.5900 (close to the constants of 3-methyldiphenyl: b.p. 148-150° at 20 mm; n_D^{20} 1.5916 [11]). It was oxidized by the method described above. Acidification of the concentrated filtrate brought down a white precipitate which after recrystallization from dilute alcohol melted at 161-162° and did not depress the melting point of 3-phenylbenzoic acid [7].

Reduction of (II). To a solution of 4 g of (II) in 30 g 80% acetic acid was added 15 g fine iron filings, and the whole heated on a boiling water bath with constant stirring for 8 hours. The reaction mixture solidified to a slurry which was brought into solution again by addition of 50 ml water. For completion of the reaction, the mixture was stirred without heating for a further hour and then treated with 30% sodium hydroxide solution until strongly alkaline. The amine was distilled off from the reaction mixture with steam and collected in dilute hydrochloric acid (1:2). The hydrochloric acid solution was evaporated to a small volume and the white precipitate recrystallized from a mixture of methyl alcohol and butyl acetate. The beautiful silvery needlets of the hydrochloride melted at 268-270°. Beilstein test positive.

0.1015 g substance: 5.6 ml N_2 (21°, 761 mm). Found %: N 6.39. $C_{13}H_{18}NCl$. Calculated %: N 6.28.

3. 2,5-Dimethyl-6-phenyl-1-nitro-Δ^3-cyclohexene (III). 5 g (0.03 mole) β-nitrostyrene, 8.5 g (0.09 mole) 2,4-hexadiene and 0.1 g hydroquinone are heated in sealed tubes for 16 hours at 150-155°. After distilling off the excess of hexadiene, the residue is fractionated in vacuum to give 6.36 g of (III) (82.6% in the form of a thick, yellow oil, strongly irritating the mucous membranes, b.p. 149-151° at 4 mm; d_4^{20} 1.1050; n_D^{20} 1.5422; MR_D 65.82; calculated 65.87.

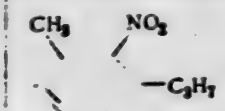
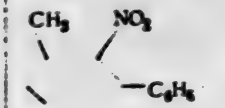
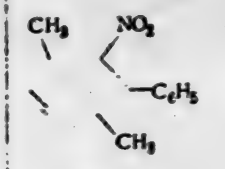
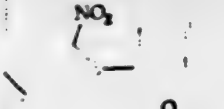
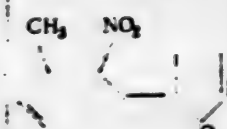
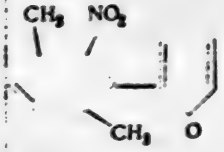
0.0404 g substance: 2.3 ml N_2 (23°, 760 mm). Found %: N 6.54. $C_{14}H_{17}O_2N$. Calculated %: N 6.60.

Reduction of (III) was performed in exactly the same manner as that of (II). There was obtained the hydrochloride of 2,5-dimethyl-6-phenyl-Δ^3-cyclohexenylamine in the form of a white, finely crystalline powder with m.p. 290-292° (from alcohol).

0.1017 g substance: 6.3 ml N_2 (19°, 747 mm). Found %: N 7.15. $C_{14}H_{20}NCl$. Calculated %: N 6.96.

4. 1-Nitro-6-(α)-furyl-Δ^3-cyclohexene (IV). 5 g (0.03 mole) furylnitroethylene [12], 6 g (0.09 mole) butadiene and 0.1 g hydroquinone were heated in sealed tubes for 10 hours at 150°. Considerable resinification was observed. After driving off the excess of butadiene the residue was fractionated to give 3.18 g (45.6%) of (IV) in the form of a yellow oil which very quickly darkened in the air and strongly irritated the mucous membranes: b.p. 148-150° at 200 mm; d_4^{20} 1.1970; n_D^{20} 1.5350; MR_D 50.21; calculated 49.91.

0.1956 g substance: 12.4 ml N_2 (22°, 753 mm) Found %: N 7.27. $C_{10}H_{11}O_3N$. Calculated %: N 7.25.

Prep. No.	Adduct	Reaction conditions (diene : dienophile)	B.p.	n_D^{20}	d_4^{20}	MR_D found	MR_D calculated	Yield (%)
I		Without solvent, 150° 15 hours (3:1)	108-110° at 6 mm	1.4728	1.0030	51.19	51.40	70
II		Without solvent, 150° 10 hours (3:1)	M.p. 80-82°	—	—	—	—	87
III		Without solvent, 155° 16 hours (3:1)	149-151 at 4 mm	1.5422	1.1050	65.82	65.87	82.6
IV		Without solvent, 150° 10 hours (3:1)	148-150 at 200 mm	1.5350	1.1970	50.21	49.91	45.6
V		Without solvent, 150° 8 hours (3:1)	120-122 at 4 mm	1.5150	1.1550	54.30	54.53	55
VI		Without solvent, 150° 16 hours (3:1)	125-127 at 4 mm	1.5191	1.1411	59.08	59.15	45.6

5. 2-Methyl-6 (α)-furyl-1-nitro-Δ^3-cyclohexene (V) 5 g (0.03 mole) furylnitroethylene, 7.2 g (0.09 mole) piperylene and 0.1 g hydroquinone were heated in sealed tubes for 8 hours at 150°. Fractionation gave 4 g (55%) of (V) in the form of a light-yellow oil, rapidly oxidizing in the air; b.p. 120-122° at 4 mm; d_4^{20} 1.1550; n_D^{20} 1.5150; MR_D 54.30; calculated 54.53.

0.0743 g substance: 5.4 ml N_2 (21°, 752 mm). Found %: N 6.73. $C_{11}H_{13}O_3N$. Calculated %: N 6.49.

6. 2,5-Dimethyl-6-(α)-furyl-1-nitro-Δ^3-cyclohexene (VI). 5 g (0.03 mole) furylnitroethylene, 9 g (0.09 mole) 2,4-hexadiene and 0.1 g hydroquinone were heated in sealed tubes for 16 hours at 150°. Vacuum fractionation yielded 3.6 g (45.6%) of (VI) in the form of a yellow oil which quickly darkened in the air; b.p. 125-127° at 4 mm; d_4^{20} 1.1411; n_D^{20} 1.5191; MR_D 59.08; calculated 59.15.

0.0836 g substance: 4.7 ml N_2 (20°, 752 mm). Found %: N 6.50. $C_{12}H_{15}O_3N$. Calculated %: N 6.30.

SUMMARY

1. Reactions were carried out on the diene synthesis of piperylene with nitroamylene, nitrostyrene, and furylnitroethylene, and of butadiene with furylnitroethylene, and 6 new cyclohexene derivatives are described.

2. For the first time furylnitroethylene has been used as a dienophile.

3. By demonstrating the structure of the adducts of piperylene with nitroamylene and nitrostyrene, it was shown that the order of addition of these dienophiles to piperylene is in good accord with the direction of polarization of piperylene and the dienophile.

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Received July 1, 1952

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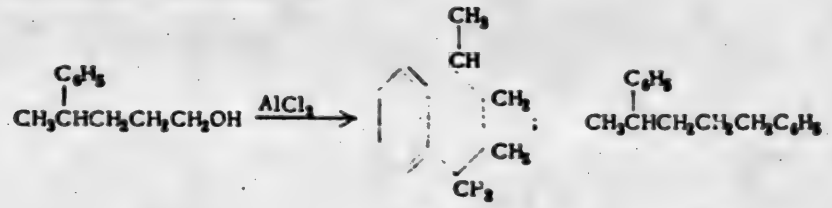
ALKYLATION OF AROMATIC COMPOUNDS WITH ALCOHOLS

XVI. CONDENSATION OF 1,4-PENTANEDIOL WITH BENZENE

I. P. Tsukervanik and N. I. Bogdanova

Studies in our laboratory of the reactions of alkylation of aromatic compounds with difunctional reactants have shown the possibility of utilization of the greater activity of the secondary hydroxyl group of 1,3-butanediol. This enabled us to realize the hydroxyalkylation of a series of aromatic compounds [1]. In the further development of this investigation we have undertaken a study of the condensation of 1,4-pentanediol with benzene. In this case we may expect the formation of 4-pheny lpentan-1-ol (I) which must readily cyclize to 1-methyltetrahydronaphthalene (II)



(I) (II) (III)

Since such a cycloalkylation is always observed in similar cases, the formation in the second stage of the condensations of 1,4-diphenylpentane (III) is less probable.

We performed a series of condensations of 1,4-pentanediol with benzene in presence of $AlCl_3$. In accordance with the mechanism of these condensations [2] it is necessary to use not less than 2 moles of $AlCl_3$ per mole of diol. By suitable choice of reaction conditions we showed the possibility of preparation of products (I) and (II) with a preponderance of one of these. 4-Phenylpentan-1-ol (I) is obtained in about 63% yield by operating with highly dilute benzene at room temperature; this was accompanied by 1-methyltetrahydronaphthalene (II) in 15% yield. When operating at higher temperatures (65-85°) the main product is (II) (50% of theory), while alcohol (I) is obtained in only 10% yield. Direct experiment showed that when 4-phenylpentanol was heated (75-85°) in benzene with $AlCl_3$, a high yield of 1-methyltetrahydronaphthalene is obtained. We were unable to find 1,4-diphenylpentane in a number of the products of alkylation, although small amounts of higher boiling fractions were isolated.

EXPERIMENTAL

1,4-Pentanediol was prepared by reduction of acetopropyl alcohol with sodium amalgam [3]. Yield 70% of the theoretical. B.p. 218-220°.

1. Reactants. 1,4-pentanediol 7.3 g (0.07 mole), benzene 150 ml, $AlCl_3$ 21 g (0.16 mole). The $AlCl_3$ was introduced in small portions, over a period of an hour, into the benzene-diol mixture with constant stirring. The mixture was held at 35-40° for 9 hours and then at 20-21° for 15 hours. After decomposition with water, the benzene layer was separated, dried and fractionated. There were obtained: 1-methyltetrahydronaphthalene 1.5 g (15% of theory), b.p. 105-110° at 18 mm; 4-phenylpentan-1-ol 7.2 g (62.5% of theory), b.p. 140-147° at 18 mm.

2. Reactants: 1,4-pentanediol 10.4 g (0.1 mole), benzene 100 ml, $AlCl_3$ 27 g (0.2 mole). After slow introduction of $AlCl_3$, the mixture was heated for 4 hours on the water bath at 75-85° and the products were: 1-methyltetrahydronaphthalene 7.6 g (52% of theory) and 4-phenylpentan-1-ol 2.6 g (16% of theory).

3. Reactants: 4-phenylpentan-1-ol 18.1 g (0.11 mole), benzene 50 ml, $AlCl_3$ 15.7 g (0.12 mole). After introduction of the $AlCl_3$ the mixture was heated for 4 hours at 75-85°. 1-Methyltetrahydronaphthalene with b.p. 105-107° at 18 mm was obtained. Yield 5 g (69% of theory).

The products of several condensations were subjected to repeated fractionation.

1-Methyltetrahydronaphthalene [4]—b.p. 88-89° (10 mm): n_D^{20} 1.5210; d_4^{25} 0.9539.

0.0982, 0.1322 g substance: 0.3238, 0.4367 g CO_2; 0.0844, 0.1143 g H_2O. Found %: C 88.98, 90.16; H 9.62, 9.67. $C_{11}H_{14}$. Calculated %: C 90.35; H 9.65.

Oxidation with nitric acid (sp.gr. 1.15) in sealed tubes at 130-150° gave phthalic acid with m.p. 188-189°. 1-Methylnaphthalene [5] was prepared by heating 1-methyl tetrahydronaphthalene with sulfur at 180-200° for 7 hours [6]. B.p. 108-109° (10 mm): n_D^{20} 1.6165; d_4^{20} 1.0192.

Picrate: m.p. 138° [7].

The same results were got in dehydrogenation of the product of experiment 3.

4-Phenylpentan-1-ol [8]. An oily liquid with a pleasant odor, b.p. 127-128° (8 mm): n_D^{20} 1.5170; d_4^{20} 0.9815.

Found %: C 80.24; H 9.85. $C_{11}H_{14}O$. Calculated %: C 80.46; H 9.85.

Passage of the vapor of 4-phenylbutanol in a vacuum (30 mm) over copper gauze at 240-260° [1] led to formation of a mixture of the initial alcohol and aldehyde. A small quantity of 4-phenylbutanol, isolated via the bisulfite compound, was converted into the dinitrophenylhydrazone with m.p. 96-97°.

4.92 mg substance: 0.775 ml N_2 (30°, 721.5 mm). Found %: N 16.60. $C_{17}H_{18}O_4N_4$. Calculated %: N 16.36.

SUMMARY

1. It is shown that in the condensation of 1,4-pentanediol with benzene the secondary hydroxyl group reacts in the first instance. The resultant 4-phenylpentan-1-ol cyclizes to 1-methyltetrahydronaphthalene on heating with excess of $AlCl_3$.

2. By conducting the condensation under selected conditions, it can be directed in one direction or the other as desired.

3. The described condensations may serve as a preparative method of synthesis of 4-phenylpentan-1-ol (63% of theory) and of 1-methyltetranydronaphthalene (52% of theory).

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Received December 15, 1952

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CHARACTERISTICS OF THE BROMINATION OF PHENYLTRICHLOROSILANE

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From the extremely small number of publications in the field of halogenation of aromatic silanes, we know that the action of halogens on aromatic organosilicon compounds may proceed in two directions. Thus the action of bromine on tetraphenylsilane [1] is accompanied not by bromination but by cleavage of the phenyl group. A similar reaction has been observed when bromine acts on p-bistriethylphenylsilane in presence of iron [2]. On the other hand, the action of chlorine on triethylphenylsilane led to triethylchlorophenylsilane [3]. Similarly, the action of chlorine on diphenyldichlorosilane and on phenylmethyldichlorosilane in presence of $FeCl_3$, $SbCl_3$ or $SbCl_5$ as catalyst at 70-120° gave chlorinated aromatic silanes containing chlorine atoms in the benzene rings [4]. These data are all that have been reported about the action of halogens on aromatic organosilicon compounds and about the products of such reactions. More detailed information, both about properties and preparative methods, is available for such compounds as p-chloro- and p-bromophenyltrichlorosilanes, di-(p-bromophenyl)-dichlorosilane, which have been synthesized with the help of appropriate organomagnesium compounds [2,5]. But the latter route cannot lead to aromatic silanes containing one or more halogen atoms in the nucleus.

We have undertaken an investigation of the halogenation of some aromatic silanes and of the properties of the resultant halo derivatives because the above survey shows the extent to which this field of chemistry has been neglected. In this paper we describe the results of syntheses of bromo derivatives of phenyltrichlorosilane. Bromination of phenyltrichlorosilane was performed in presence of the usual catalysts employed in halogenation of aromatic compounds (metallic iron, $SbCl_3$). It was established that the action of bromine on phenyltrichlorosilane in presence of metallic iron is accompanied by a vigorous exothermic reaction. At 45-50° the bromination proceeds fairly intensively and the bromine is completely taken up by the reaction mixture. Using a phenyltrichlorosilane/bromine ratio (molar) of 1:0.76, the main reaction product is monobromophenyltrichlorosilane, which is obtained in a yield of 90% of the theoretical, calculated on the reacted phenyltrichlorosilane:

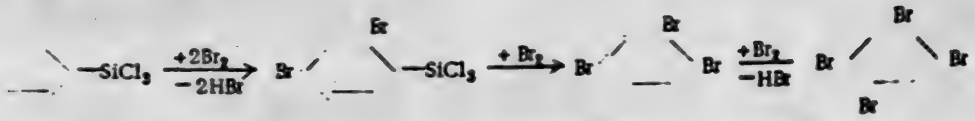
$$C_6H_5SiCl_3 + Br_2 \longrightarrow C_6H_4BrSiCl_3 + HBr.$$

Continuance of bromination at the same temperature (molar ratio of reactants 1:1.82) leads to formation of dibromophenyltrichlorosilane in a yield of about 70% of the theoretical (with an over-all yield of about 80% based on the bromophenyltrichlorosilanes). A distinguishing feature of the latter reaction is that substitution is accompanied by a secondary reaction involving cleavage of products at the Si—C bond. The cleavage products are, on the one hand, a silicon-containing compound (apparently $SiCl_3Br$) and, on the other hand, a brominated benzene (p-dibromobenzene, isolated pure). Consequently the bromination of phenyltrichlorosilane at this stage proceeds according to the scheme:

$$C_6H_4BrSiCl_3 + Br_2 \begin{cases} \longrightarrow C_6H_3Br_2SiCl_3 + HBr \text{ (main reaction)} \\ \longrightarrow SiCl_3Br + p\text{-}C_6H_4Br_2 \text{ (side reaction)} \end{cases}$$

Due to the occurrence of the side reaction (destructive bromination) the yield of dibromophenyltrichlorosilane is reduced.

Destructive bromination proved to be the sole reaction taking place in attempts to prepare tribromophenyltrichlorosilane. In this case the bromination proceeds at a considerably lower speed than in the preparation of the mono- and dibromo- derivatives, and necessitates prolonged action of excess of bromine on phenyltrichlorosilane at 80-90°. Thus, with a ratio of reactants of 1:3.25 the principal reaction product is 1,2,4,5-tetrabromobenzene, side by side with dibromophenyltrichlorosilane which is obtained in a yield of 24.6% of the theoretical. No trace of tribromophenyltrichlorosilane could be found among the reaction products. Formation of 1,2,4,5-tetrabromobenzene may be represented by the following scheme:



This scheme could be confirmed to some extent by experiments on the bromination of 2,4-dibromophenyltrichlorosilane. Thus, on conducting the bromination of 2,4-dibromophenyltrichlorosilane (molar ratio of $C_6H_3Br_2SiCl_3/Br_2$ approx. 1:2) in presence of metallic iron at 90-95°, only a small amount of 2,4-dibromoderivative is recovered unchanged; in this case the main reaction product is 1,2,4,5-tetrabromobenzene, formed in good yield.

The complete absence from the reaction products of tribromophenyltrichlorosilane as well as of 1,2,4,6-tetrabromobenzene permits the assumption that the Si—C bond is cleaved in dibromophenyltrichlorosilane under the action of bromine and that tribromophenyltrichlorosilane is apparently not formed, even as an intermediate product. Attempts to obtain tribromophenyltrichlorosilane by bromination of 2,4-dibromophenyltrichlorosilane in milder conditions (in carbon tetrachloride solution at 75-77°) did not attain their objective (substantially the whole of the dibromophenyltrichlorosilane was recovered unchanged). A positive result did not follow the bromination of the dibromo-derivative in presence of 2% antimony trichloride as catalyst even at 180-200°.

Consequently, the course of the bromination of phenyltrichlorosilane in presence of catalysts depends on the nature of the catalyst, on the thermal conditions of the reaction and on the ratio of reactants. It should be noted that in the absence of catalysts the bromination of phenyltrichlorosilane does not take place even at 170-180° (in a sealed tube).

The structure of the synthesized bromo derivatives of phenyltrichlorosilane was confirmed with the help of cleavage reactions in presence of aluminum chloride and bromine water. The first of these reactions was previously reported by various authors [6] for unsubstituted aromatic silanes such as tetraphenylsilane, triethylphenylsilane and diphenyldichlorosilane. But the cleavage of the Si—C bond with the help of bromine water has only been described in the case of quaternary aromatic nitro-substituted organosilicon compounds [7]. In their application to bromosubstituted phenyltrichlorosilanes, these reactionsare here studied for the first time. In these cases the reaction proceeds in such a manner that the products of the cleavage reactions are bromo derivatives of benzene, e.g.:

$$C_6H_3Br_2SiCl_3 + AlCl_3 \xrightarrow{(5H_2O)} C_6H_4Br_2 + SiO_2 + 6HCl + Al(OH)_3$$

$$C_6H_3Br_2SiCl_3 + Br_2 + 2H_2O \longrightarrow C_6H_3Br_3 + SiO_2 + 3HCl + HBr,$$

and it is possible to evaluate their structure both in respect to the relative positions of the bromine atoms in the aromatic ring of bromophenyltrichlorosilane and in respect to the orienting effect of the silicyl chloride group. It was thus established that although the $SiCl_3$ group must, by its nature, be a meta-orienting substituent, the bromination of phenyltrichlorosilane in presence of iron leads to formation exclusively of the para-derivative. Formation of a para- and not a meta-derivative is confirmed beyond doubt by the fact that the product of cleavage of monobromophenyltrichlorosilane with bromine water (heating at 150-160° in a sealed tube) is p-dibromobenzene (yield 83% of the theoretical); further confirmation is supplied by the identity between the bromination product and the p-bromophenyltrichlorosilane prepared from p-bromophenyl magnesium bromide and silicon tetrachloride:

$$p\text{-}BrC_6H_4MgBr + SiCl_4 \longrightarrow p\text{-}BrC_6H_4SiCl_3 + MgBrCl.$$

These results clearly demonstrated an anomalous course of reactions involving substitution of hydrogen atoms by bromine atoms in the phenyltrichlorosilane ring under the action of elementary bromine in presence of a catalyst. Investigation of the structure of dibromophenyltrichlorosilane fully confirmed this fact: when the latter was cleaved with bromine water (heating at 180-190° in a sealed tube) the reaction product was 1,2,4-tribromobenzene (60% yield); cleavage of dibromophenyltrichlorosilane with aluminum chloride (using a 1:1 molar ratio of components) led to formation of m-dibromobenzene in 55% yield. These data indicate that the dibromoderivative of phenyltrichlorosilane prepared by bromination of the latter in presence of a catalyst is 2,4-dibromophenyltrichlorosilane. Here again, therefore, we observe an anomalous orientation of the bromine atoms entering the nucleus of phenyltrichlorosilane.

EXPERIMENTAL

I. Preparation of p-bromophenyltrichlorosilane. The reaction vessel was a four-necked round-bottomed flask fitted with a mechanical stirrer, a dropping funnel, a thermometer and a reflux condenser connected to a series of absorption bottles intended for trapping the hydrogen bromide. Into this vessel was introduced 100.0 g (0.472 mole) phenyltrichlorosilane and 0.5 g powdered metallic iron (0.5% of the weight of the phenyltrichlorosilane). Addition was made to this mixture, with stirring, over a period of 1½-2 hours, of 58.0 g (0.362 mole) dry bromine (dropwise from the dropping funnel); this was 76.7% of the amount of bromine theoretically required for bromination to the monobromo-derivative. After 1-2 minutes the temperature of the reaction mass began to rise and reached 50°. Intensive bromination took place at 45-50°, and substantially the whole of the bromine entered into reaction. When all had been added, the reaction mass was heated for one hour on a water bath at 90-95° for completion of the reaction, after which a stream of dry air was passed through for removal of the residue of hydrogen bromide and unreacted bromine. The weight increase after the air-blowing was 26.1 g (against 28.6 g theoretically demanded for bromination to the monobromo-derivative in the conditions of this experiment). The amount of hydrogen bromide evolved as a result of bromination was 27.7 g.

Vacuum-distillation of the bromination product gave: 1) b.p. 68-90° (6 mm) — 26.3 g; 2) b.p. 90-115° (6 mm) — 97.2 g; flask residue about 2.0 g of dark resin.

The first fraction was mainly unchanged phenyltrichlorosilane. Redistillation of the second fraction gave 94.8 g colorless liquid with b.p. 105-109° (6 mm) which consisted of monobromophenyltrichlorosilane. Yield 69% of the theoretical, calculated on the reacted phenyltrichlorosilane.

Monobromophenyltrichlorosilane is a colorless, mobile, oily liquid fuming in the air: b.p. 106-108° (6 mm), d^{20} 1.6771. For the purpose of determination of the bromine content, a small amount of the obtained monobromophenyltrichlorosilane was resinified by treatment with water and subjected to analysis.

Found %: Br 38.0, 38.5; Cl (hydrolysis) 36.3, 36.1. $C_6H_4BrSiO_{1.5}$. Calculated %: Br 38.4. $C_6H_4BrSiCl_3$. Calculated %: Cl (hydrolysis) 36.6.

The properties of the obtained monobromophenyltrichlorosilane were identical with those of synthetic p-bromophenyltrichlorosilane prepared from p-bromophenyl magnesium bromide and silicon tetrachloride. In addition, evidence of the structure was obtained by cleavage with bromine water in a sealed tube. Into a glass tube were introduced 2.0 g monobromophenyltrichlorosilane, 0.9 ml bromine and 1.9 ml water. The tube was heated in a tube furnace for 6 hours at 150-160°. The contents of the tube were then extracted with ether and the ether extract was washed with 10% sodium carbonate solution; the solution was then washed with water and dried over calcium chloride. From the ether extract was isolated a crystalline, white substance which was recrystallized twice from alcohol to form lustrous, white platelets with m.p. 86.2°, consisting of p-dibromobenzene (about 1.3 g). It did not depress the m.p. of p-dibromobenzene. Yield of p-dibromobenzene about 83% of the theoretical.

II. Preparation of 2,4-dibromophenyltrichlorosilane. Bromination of phenyltrichlorosilane to the dibromo derivative was performed in the same conditions as above except that the amount of bromine brought into reaction was correspondingly increased. Into a mixture of 100.0 g (0.472 mole) phenyltrichlorosilane and 0.5 g metallic, powdered iron (0.5% of the weight of the phenyltrichlorosilane) was introduced dropwise, with stirring over a period of 2½-3 hours, 138.0 g (0.862 mole) dry bromine, equivalent to 91.2% of the theoretical amount for bromination to the dibromo derivative. During the period of introduction the temperature of the reaction mass was held at 45-50°, following which the reaction was completed by heating for one hour on a water bath at 90-95°. The amount of hydrogen bromide evolved during the reaction was 57.4 g.

Vacuum-distillation of the bromination product gave: 1) b.p. 85-125° (6 mm) — 22.0 g; 2) b.p. 125-150° (6 mm) — 130.0 g; residue in flask about 2.0 g of dark resin.

On distillation of the first fraction, crystallization in the condenser occurred at the very start (needles). This fraction was treated with water and subjected to steam distillation. From the distillate was isolated a white crystalline substance (4.0 g) which after two recrystallizations from alcohol formed white leaflets with m.p. 86.2°. This substance did not depress the m.p. of p-dibromobenzene.

Found %: Br 67.2, 67.4 (Carius method) $C_6H_4Br_2$. Calculated %: Br 67.8.

The residue in the flask (10.5 g) after the steam distillation was a light-yellow, transparent resin whose bromine and silicon contents were consistent with the formula $(C_6H_4BrSiO_{1.5})_n$. Formation of this resin would be due to saponification of the monobromophenyltrichlorosilane present in the first fraction.

Found %: Br 37.6, 37.5; Si 13.0, 12.6. $(C_6H_4BrSiO_{1.5})_n$. Calculated %: Br 38.4; Si 13.46.

Consequently the first fraction contained p-dibromobenzene in addition to monobromophenyltrichlorosilane.

Redistillation of the second fraction gave 122.0 g liquid with b.p. 143-147° (6 mm), consisting of dibromophenyltrichlorosilane. Yield 70% of the theoretical, calculated on the phenyltrichlorosilane taken in the reaction.

Dibromophenyltrichlorosilane is a colorless, mobile, oily liquid, which fumes in the air; b.p. 144-146° (6 mm), d^{20} 1.9502. A portion of the prepared substance was analyzed for bromine by treating with water and estimating the bromine content of the resultant resin.

Found %: Br 55.4, 55.8 (Carius); Cl (hydrolysis) 28.4, 28.6. $C_6H_3Br_2SiO_{1.5}$. Calculated %: Br 55.7. $C_6H_3Br_2SiCl_3$. Calculated %: Cl (hydrolysis) 28.8.

The total yield of bromophenyltrichlorosilanes (mono- and dibromo- derivatives) was about 80% of the theoretical.

The structure of the prepared dibromophenyltrichlorosilane was confirmed by cleavage with bromine water. A sealed glass tube containing 2.0 g dibromophenyltrichlorosilane, 0.5 ml bromine and 1.2 ml water was heated for 6 hours at 180-190°. The contents of the tube were then worked up as described above. From the ether extract was isolated a crystalline compound which after two recrystallizations from alcohol-ether mixture gave white needles with m.p. 44°, consisting of 1,2,4-tribromobenzene (1.0 g) in a yield of 60% of the theoretical).

For further confirmation, the dibromophenyltrichlorosilane was cleaved with $AlCl_3$ (1:1 ratio of reactants). The reaction product (after decomposition of the reaction mass with water) was m-dibromobenzene – a liquid with b.p. 220°, solidification point 7°, and d^{20} 1.9594 (yield 55% of the theoretical).

III. Attempts to prepare tribromophenyltrichlorosilane. 1. Bromination of phenyltrichlorosilane. To a mixture of 35.0 g (0.165 mole) phenyltrichlorosilane and 0.17 g powdered metallic iron (0.5% of the weight of the phenyltrichlorosilane) was added dropwise, with stirring, 85.8 g (0.536 mole) dry bromine (silane/bromine ratio - 1:3.25). The first two-thirds of the bromine was added in the course of 1½ hours at 45-50° and substantially the whole of it entered into reaction. Since the further progress of the reaction was appreciably slowed down, the last third of the bromine was added over a period of 1½ hours at 75-80°. After the whole of the bromine had been added, the reaction was completed by heating for one hour on the water bath at 90-95°. With progressive cooling the bromination product partially crystallized. The weight increase of the reaction mass after air-blowing was 38.0 g. The amount of hydrogen bromide evolved as a result of bromination was 38.1 g (a precipitate of SiO_2 was observed in the bottle in which the hydrogen bromide was absorbed).

Vacuum-distillation of the bromination product gave: 1) b.p. 135-155° (6 mm) – 20.0 g; 2) b.p. 155-165° (6 mm) – 45.0 g; residue in flask about 5.0 g of dark resin.

The first fraction is an oily liquid containing a small amount of crystals (about 3 g) of tetrabromobenzene. Examination of this fraction showed it to consist mainly of dibromophenyltrichlorosilane (about 15.0 g).

The second fraction crystallized almost completely at the ordinary temperature but the crystals were permeated by an oily liquid. Two recrystallizations from dry dichloroethane (or petroleum ether) gave white needles (about 38.0 g) with m.p. 175° and the specific odor of polyhalobenzenes. Analysis revealed the absence from it of silicon and hydrolyzable chlorine, while the bromine content (Carius) corresponded to that of tetrabromobenzene.

Found %: Br 80.7, 81.0. $C_6H_2Br_4$. Calculated %: Br 81.2.

The m.p. of 175° agreed with that of 1,2,4,5-tetrabromobenzene.

2. Bromination of 2,4-dibromophenyltrichlorosilane. a) To a mixture of 20.0 g (0.054 mole) 2,4-dibromophenyltrichlorosilane (prepared as described above) and 0.1 g powdered metallic iron was added dropwise, over a period of 0.5 hours, 17.2 g (0.107 mole) dry bromine (silane/bromine ratio = approx. 1:2.0). The reaction only took place with evolution of hydrogen bromide when the mass was heated to 90-95°. Heating was therefore performed on the boiling water bath for one hour. On cooling, the bromination product crystallized.

Vacuum-distillation gave: 1) b.p. 140-160° (7 mm) —4.0 g, 2) b.p. 160-170° (7 mm) —16.0 g; residue in flask about 2 g dark resin.

The first fraction, an oily liquid partly crystallizing on cooling, was found to consist mainly of unchanged dibromophenyltrichlorosilane with an admixture of bromo-derivatives of benzene.

Redistillation of the second fraction yielded about 14.5 g colorless, transparent liquid with b.p. 163-165° (7 mm) which rapidly crystallized. Two recrystallizations from petroleum ether gave white needles melting at 175-176° (about 9.0 g). The analysis was consistent with the compound being a tetrabromobenzene. It did not depress the melting point of 1,2,4,5-tetrabromobenzene.

b) Bromination of dibromophenyltrichlorosilane did not take place on heating a mixture of 15.0 g (0.04 mole) 2,4-dibromophenyltrichlorosilane, 45.0 g carbon tetrachloride, 0.08 g iron powder and 7.7 g (0.048 mole) bromine at 75-77°. When the mixture was fractionated the dibromo compound was recovered unchanged (14.0 g).

c) Heating for two hours of a mixture of 15.0 g (0.04 mole) 2,4-dibromophenyltrichlorosilane, 0.03 g $SbCl_3$ and 9.7 g (0.06 mole) bromine at 180-200° did not result in bromination of the silane. Fractionation of the reaction mixture gave 14.5 g of the original dibromophenyltrichlorosilane.

SUMMARY

1. The following results were obtained in a study of the reaction of bromine with phenyltrichlorosilane: a) in the absence of catalyst no reaction occurs even at 200°; b) in the presence of the usual catalysts for halogenation of aromatic compounds, for example iron, ring-bromination takes place relatively easily up to formation of the dibromo-derivative. It was not possible to prepare a tribromo-derivative by bromination of phenyltrichlorosilane or of dibromophenyltrichlorosilane in presence of iron or antimony trichloride.

2. The reaction of formation of bromophenyltrichlorosilanes is accompanied by the side reaction of destructive bromination as represented by cleavage by bromine of the Si—C bonds of organosilicon compounds. It was noted that the course of this side reaction depends on the nature of the catalyst.

3. Of the products of bromination of phenyltrichlorosilane, the mono- and dibromo-derivatives were isolated in good yields and characterized in the pure form. Their structures correspond respectively to 1,4- and 1,2,4-isomers.

4. Bromination of phenyltrichlorosilane in presence of catalysts is found to proceed anomalously in respect to the orienting effect of the $SiCl_3$ group. In place of the anticipated meta-orientation there was observed the unusual ortho-para-orientation of the bromine atoms entering the nucleus.

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Received September 21, 1952.

CARBOXYLIC ANHYDRIDES OF AMINO ACIDS AS A STRUCTURAL FRAGMENT IN THE PROTEIN MOLECULE

(Commemoration of the 60th anniversary of A. Ya. Danilevsky's theory of elementary series)

L. N. Akimova and N. I. Gavrilov

After demonstrating in a series of papers that the polypeptide theory is no longer consistent with the experimental facts [1] accumulated by numerous workers over the past 20 years, we shall now attempt on the basis of model syntheses to identify the possible fragments of the protein structure corresponding to natural proteins in properties and capable of facilitating the clarification of protein structure. These fragments include the bond reported in 1891 by the founder of Russian biochemistry, A. Ya. Danilevsky [2]. The reality of the carboanhydride bond discovered by him was experimentally established in 1924 by Fränkel [3].

By the eighties of last century a hundred years had already passed since the establishment of the elementary composition of proteins and since the significance of the amino acids for their structure had been demonstrated. At that time potein was characterized as a complex mixed anhydride of a relatively small number of amino acids (not more than twenty--Schall, Grimaux, Schützenberger). This period also marked the start of attempts to synthesize protein from amino acids. It was perfectly natural that in the attempts to gain insight into the structure of the protein molecule, investigators should work along the lines of combining amino acids among themselves in such a manner that compounds possessing all the properties of the natural products would be formed. And since a number of workers tended to characterize protein as amino acid anhydrides, it is fully understandable why the first syntheses were directed to the preparation of such anhydrides. In view of the fact that most anhydrides are prepared by removal of water, use was made of the usual methods of dehydration, consisting in the heating of the amino acid or mixtures of amino acids in glycerol or with P_2O_5, or in treatment with thionyl chloride. The first to synthesize these anhydrides was the German chemist Curtius [4]. He prepared the first anhydride $C_6H_5CONHCH_2CONHCH_2COOH$ (hippurylglycine). This synthesis was especially interesting in that hippuric acid was a member of the group of natural compounds since it is found in horses' urine. This synthesis initiated a whole series of investigations with a view to synthesis of protein. It was thus shown for the first time that amino acids can combine with one another at the substituted amino bond, subsequently named the peptide bond by Fischer.

In 1883 Curtius drew attention to the fact that the ethyl ester of glycine undergoes spontaneous transformation into glycine anhydride (diketopiperazine) and a substance giving a positive biuret reaction. For this reason the latter substance was called "biuret base". Later work by Curtius showed that if moisture was removed from the reaction mixture, the anhydride formation was inhibited and "biuret base" was the main reaction product. But Curtius' erroneous theory about the occurrence of the biuret reaction of proteins did not permit him to put forward a theory of the structure of synthetic "biuret base". And it was only after a further 21 years that this substance was conclusively identified as a pentapeptide ether.

All the above attempts at a protein synthesis were not linked by common concepts of the structure of protein. The diversity of amino acids in protein and the high molecular weight very seriously complicated the problem of elucidating the structures of proteins and have so far prevented a systematic synthesis of these compounds. Evidence of this is provided by the fact that nobody has yet (with the exception of Rinch and Talmud) presented a general theory of protein structure, discussions ranging only round protein fragments and the indeterminate protein structures proposed by Astbury and Pauling.

Credit for the first attempt to establish the structure of a concrete fragment of the molecular structure belongs to A. Ya. Danilevsky. He was the first to approach the problem of protein structure as an organic chemist. In attempting to establish the fundamental structural units of proteins, Danilevsky concentrated on the fact that in the decomposition of proteins in the living organism the end product of metabolism is urea; moreover, the products of digestion of proteins with gastric juice—peptone—give a pink color on addition of $CuSO_4$ and NaOH. The same color is given with these reagents by the compound formed by melting of urea (biuret). This justified Danilevsky in proposing that the molecular grouping of biuret in the form of molecules or of —NHCONHCONH—

residues is a precursor in the structure of protein. Danilovsky writes as follows: ". . .in the protein molecule the 'carboazoto' group is not actually the biuret residue, but it is a complex of atoms of carbon and nitrogen which have the same intramolecular behavior as in biuret. I therefore suggest that the biuret group of the protein molecule has the form —NHCONHCONH—".

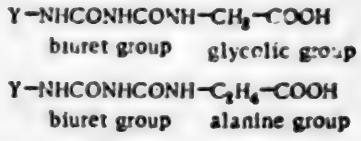
It should be noted that at that time the biuret reaction of organic compounds, which had been mainly studied with diamides, was not associated with the peptide structure of the protein molecule, and therefore also in A. Ya. Danilevsky's considerations this reaction is not identified with the polypeptide structure but with the presence in protein of biuret and amides. It must be emphasized that only E. Fischer introduced the biuret reaction as a characteristic of modern ideas of protein structure involving the presence of polypeptides. While suggesting the presence in protein of individual molecules (or, more correctly, residues) of biuret, Danilevsky sought confirmation of this suggestion by attempting to obtain biuret by hydrolyzing protein. All his efforts, however, were in vain, and his tentative suggestion was verified only after ureide acids — citrullin, etc. — had been found among the breakdown products of protein.

In what way did A. Ya. Danilevsky sense the relation between the biuret-containing groups and the main structural units of protein, i.e. amino acids? To what extent did his proposed structural micro-fragments correspond to our concepts of protein structure? A great deal has changed since that time. The polypeptide theory of Hofmeister and Fischer was developed and discarded, the diketopiperazine theory of Zelinsky and Sadikov had a salutary influence, and the ideas expounded by A. Ya. Danilevsky were not fully confirmed. But Danilevsky's ideas about elementary series have developed into the concept of the monomer in the protein structure.

Now the biuret group was the precursor of the discovery of the ureido acids. The anhydride bonds, simple and mixed, permitted the prediction of a whole series of structures found in other investigations, and their confirmation and development (the prosthetic group, the C—O—C— anhydride bond, the CO—NH—peptide bond; utilization of the biuret reaction as a criterion of structure). But A. Ya. Danilevsky was cautious. This is what he writes about his structures: ". . . each elementary series constitutes a prototype of protein substance, but is still not protein substance. . ."

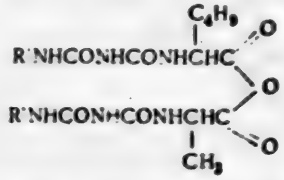
What, then does Danilevsky's elementary series consist of? In his opinion the individual biuret residues are combined with amino acids and prosthetic groups to form structural units designated by him the "elementary series of the protein molecule". The general formula of such series has the form Y—NHCONHCONH—R, where R is an amino acid residue and Y is a prosthetic group of protein and non-protein origin (carbohydrate, alkaloid, amino acid, etc.).

For example:

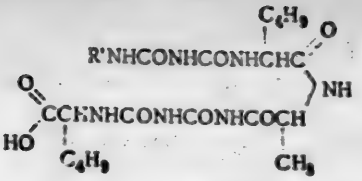


It is interesting that in this form of the compounds the amide group of biuret is simultaneously the α-amino group of the amino acid.

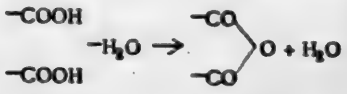
Moreover, according to Danilevsky this fragment is linked to another fragment by means of the anhydride bond and we obtain the transition to the macrostructure:



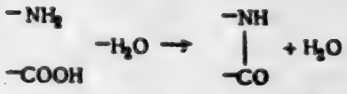
An exceptional possibility, according to Danilevsky, is the formation of an anhydride bond at an amino acid entering at the group R':



Danilevsky thus suggested the existence in the protein molecule of two types of anhydride bonds: one type —the predominating one — mainly in the form of a simple anhydride:



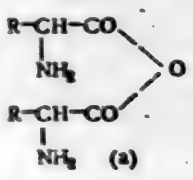
and the other possible one in the form of a mixed anhydride



This hypothesis of the occurrence of two possible types of bond in the protein molecule was supported, in Danilevsky's opinion, by the specificity of the medium necessary for the activity of ferments (acid for pepsin, and alkaline for trypsin). We may note that Danilevsky did not ascribe special significance to the mixed anhydrides, and he considered that they could be present in proteins but with a lesser degree of probability than the simple anhydrides. In this resides the fundamental distinction between Danilevsky's ideas about protein structure and the polypeptide theory which regards a bond of the mixed linear anhydride type as the principal and sole bond in proteins.

Special attention is merited by Danilevsky's concept of the anhydride bond in proteins between the microfragments which enclose the biuret group. Still another service of Danilevsky was that he was the first to approach the problem analytically and to base his hypotheses on the facts accumulated at that time, so that he was able to conclude that the protein molecule comprises microfragments which are linked to form a macromolecule. In the nineties of the last century it was clearly demonstrable that the analytical method permitted the inference that anhydrides entered into the structure of protein.

In the twenties of this century Fränkel [3] fermented protein with trypsin and isolated anhydrides of amino acids such as tyrosine, tryptophane and others, consistent with Danilevsky's ideas. When he treated protein with pancreatin he observed the formation of free tryptophane (test by reaction with bromine water). The free amino acid disappears on continuation of the treatment of protein with pancreatin or with pure preparations of trypsin. The author explains this change by the synthesizing action of the ferment; he draws attention to the following possible couplings or combinations of amino acids with one another: dipeptide — due to detachment of one molecule of H_2O; anhydride (a), also formed with loss of one molecule of H_2O; and cyclic anhydride, formed with separation of 2 molecules of H_2O. Analysis of the isolated Fränkel compounds showed that they contained two free amino groups (van Slyke determination) and that carboxyl groups were absent (Sörenson's formol titration). All this is evidence for an anhydride structure of the type of a. Fränkel's isolation of the anhydrides of tryptophane and tyrosine from proteins marked the discovery of a new function of trypsin (up to then trypsin had only been known to cleave peptide bonds), involving the anhydridization of amino acids of identical structures. Formation of mixed anhydrides was not observed during the process. Fränkel's detection of amino acid anhydrides in proteins and the elucidation of their structure by analysis permitted the prediction of the natural existence of this type of bond.

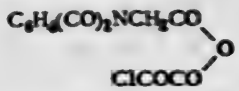


In recent years investigations have been made, in particular, of a whole series of reactions leading to the synthesis of a carboanhydride bond of a mixed type [5]. These reactions were mainly performed with N-substituted amino acids (carbobenzoxy, phthaloyl-) which were converted into mixed anhydrides under the action of ethyl chloroformate in presence of a tertiary amine in dioxane or chloroform. The resultant mixed anhydrides were not isolated but immediately entered into reaction with the amino acid to form compounds with a peptide bond. This method provided a new route to the synthesis of peptides.

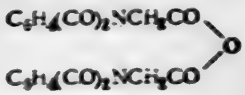
It is interesting to note that if Danilevsky had realized his structure experimentally, he would indisputably have been the founder of the theory of the peptide structure of protein. For the action of simple anhydrides, similar

to those indicated by Danilevsky, on amino acids leads (as will be shown below) to the synthesis of peptides.

In our preceding studies [6] we demonstrated the reality of the N-aminoacyl bond. In the further development of this type of compound of diketopiperazine with amino acids, it appeared to us of great interest to effect a direct synthesis of N-aminoacyldiketopiperazines containing a tripeptide. Since the action of phosphorus pentachloride on N-substituted dipeptides does not lead to the desired acid chlorides, we attempted to prepare the latter with the help of other chlorinating media. As will be shown below, we used thionyl chloride and oxalyl chloride. After unsuccessful attempts to synthesize the acid chlorides of di- and tripeptides with the help of thionyl chloride, we proceeded to investigate the chlorination reaction with oxalyl chloride. In place, however, of the anticipated acid chlorides either we obtained mixed anhydrides:



or else reactions with oxalyl chloride led to water cleavage with formation of simple anhydrides:



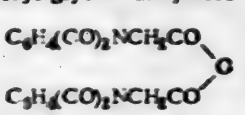
Since these simple anhydrides (judging by the studies of Danilevsky and Fränkel) can play a large part in the structure of protein, we began a study of the conditions of their formation and an investigation of their properties.

EXPERIMENTAL

I. Preparation of Simple Amino Acid Anhydrides from Mixed Anhydrides.

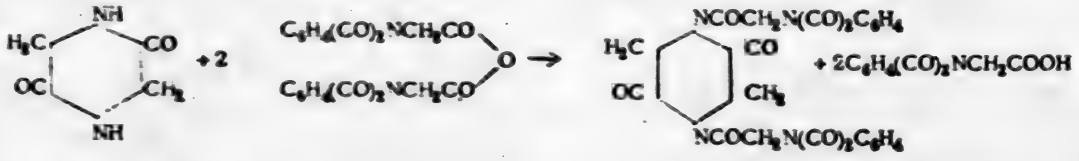
1. Chlorination of phthaloyl-glycine with oxalyl chloride in benzene. To 2 g phthaloyl-glycine in a Gavrilov tube was added 2.5 g oxalyl chloride (2 moles) and 15 ml dry benzene. Heating was carried out for 48 hours, during which period no visible changes were observed. At the end of the reaction, the precipitate was filtered and washed with benzene. After recrystallization from nitrobenzene the substance melted at 215°. The Beilstein test was negative. Yield 1.8 g (99%). The substance was assumed to be phthaloyl-glycine anhydride. We tested this assumption by carrying out the acylation of diketopiperazine.

Suggested formula — Phthaloyl-glycine anhydride



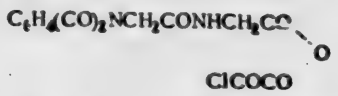
Found %: C 61.30, 61.49; H 3.36, 3.55; N 6.95, 7.14. $C_{20}H_{12}O_7N_2$. Calculated %: C 61.22; H 3.06; N 7.14.

1.1 g diketopiperazine, finely pulverized, was mixed with 3.9 g (2 moles) of the prepared phthaloyl-glycine anhydride and 15 ml nitrobenzene, and the mixture was heated on a glycerol bath at 140°. All had dissolved after 45 minutes. A precipitate came down on cooling; its properties (m.p. 385° and a positive result in the tripeptide biuret reaction after standing with caustic alkali) indicated its identity with the previously prepared N,N'-phthaloylglycyl-diketopiperazine [6]. Phthaloyl-glycine was isolated from the filtrate.



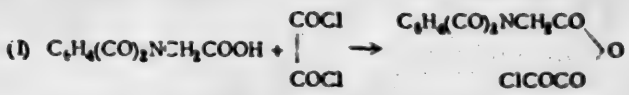
2. Chlorination of phthaloyl-glycylglycine with oxalyl chloride in benzene. 1.3 g phthaloyl-glycylglycine and 1.3 g oxalyl chloride were placed in a Gavrilov tube and 25 ml dry benzene was added. The reaction mixture was heated for 6 hours over a burner and left overnight. The precipitate was filtered and washed with benzene. The product contained halogen. It was purified by treatment with acetone, during which process a very small proportion dissolved. The insoluble residue was transferred to a flask with a reflux condenser and heated in xylene until dissolved.

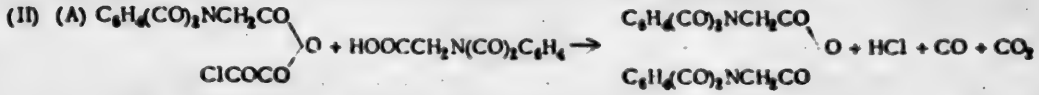
additions of xylene being made from time to time. The hot xylene solution was filtered from the insoluble residue. When the xylene solution was cooled it deposited uniform microscopic needles. The substance was insoluble in hot water, alcohol and ether, soluble in acetone; it was recrystallized from nitrobenzene and xylene; m.p. 220° with decomposition. The same substance came down from the acetone filtrate. On the basis of analysis this compound was assigned the structure of the mixed anhydride:

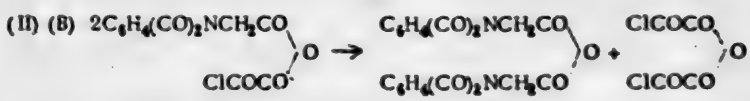


Found %: C 47.53, 47.47; H 2.41, 2.47; N 7.79; Cl 10.10. $C_{14}H_9O_7N_2Cl$. Calculated %: C 47.65; H 2.55; N 7.94, Cl 10.07.

This experiment enabled us to put forward the following mechanism of formation of the previously prepared phthaloyl-glycine anhydride, isolated from experiment 1 through the stage of formation of the mixed phthaloyl-glycine-oxalyl anhydride:

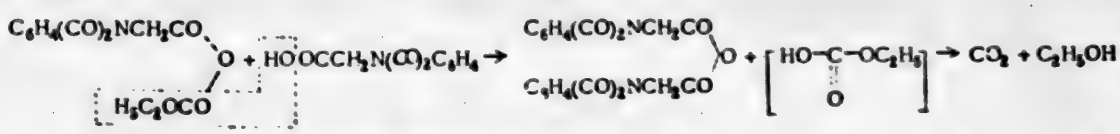






The experiments lead to the conclusion that the synthesis of simple amino acid anhydrides proceeds through the stage of the mixed anhydrides. This enabled us to make use of the recently prepared mixed amino acid anhydrides for the synthesis of simple amino acid anhydrides.

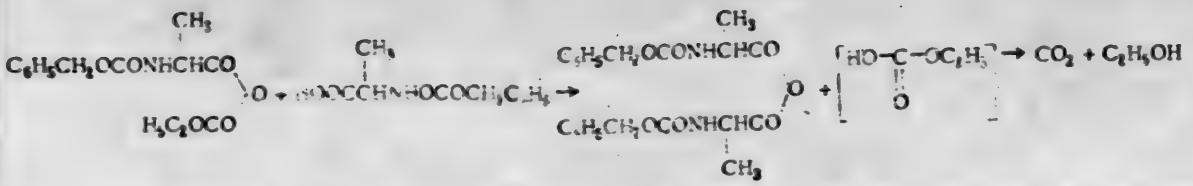
3. Preparation of phthaloyl-glycine anhydride. 0.84 g phthaloyl-glycine was dissolved in 10 ml absolute dioxane and 0.4 ml triethylamine was added. After cooling with water to 10°, addition was made of 0.4 ml ethyl chloroformate. After 10 minutes addition was made to the solution of 0.84 g phthaloyl-glycine in 10 ml absolute dioxane. Evolution of CO_2 took place. After an hour the precipitate was filtered off, washed three times with alcohol and then with ether. By its properties and m.p. (215°) the precipitate was identified as phthaloyl-glycine anhydride. It did not depress the melting-point of a specimen of the above-described phthaloylglycine anhydride. Yield 1.5 g (93% of the theoretical). Formation of phthaloylglycine anhydride proceeds according to the following scheme:



4. Preparation of carbobenzoxyalanine anhydride. 0.94 g carbobenzoxyalanine was dissolved in 5 ml absolute dioxane and 0.45 g triethylamine was added. While cooling with water, addition was made to the solution of 0.4 ml ethyl chloroformate and the mass was stood at room temperature for 10 minutes. Addition was then made of 0.94 g carbobenzoxyalanine dissolved in 5 ml absolute dioxane. The mixture was left for an hour. No visible changes appeared in the precipitate and CO_2 was evolved. After an hour the precipitate was filtered and washed a few times with alcohol and then with ether. The product was recrystallized from nitrobenzene: m.p. 143°. The crystalline form (squares) is very characteristic.

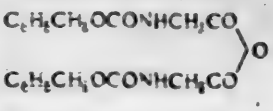
Found %: C 61.79, 61.73; H 5.65, 5.61; N 6.50, 6.60. $C_{22}H_{24}O_7N_2$. Calculated %: C 61.69; H 5.61; N 6.54.

Formation of carbobenzoxyalanine anhydride may be represented by the following scheme:



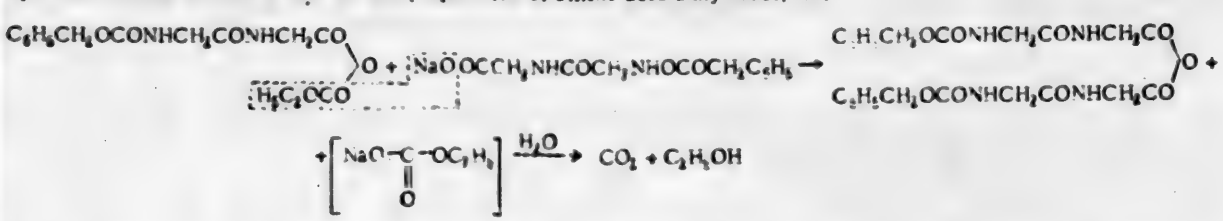
5. Preparation of carbobenzoxyglycine anhydride. 1.04 g carbobenzoxyglycine was dissolved in 5 ml absolute dioxane and 0.3 ml triethylamine was added. While cooling with water, 0.54 g ethyl chloroformate was added and the mixture left for 10 minutes at room temperature, after which 1.04 g carbobenzoxyalanine dissolved in 5 ml absolute dioxane was added. The mixture was left for an hour. Evolution of CO_2 took place. After an hour the precipitate was filtered and washed with alcohol and then with ether. The product melts at 114° after recrystallization from nitrobenzene and has the appearance of hexagonal prisms under the microscope. Yield 1.0 g or 50% of theory.

Proposed formula



Found %: C 60.11, 60.00; H 4.95, 4.86; N 6.90, 6.84. $C_{18}H_{18}O_7N_2$. Calculated %: C 59.69; H 4.99; N 7.00.

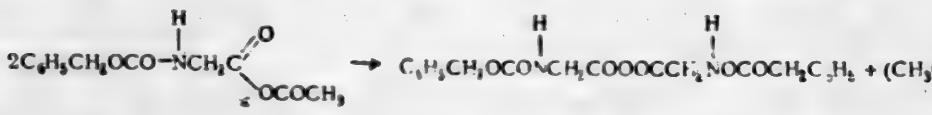
Preparation by the described method of the corresponding simple peptide-anhydrides was complicated due to the sparing solubility of the carbobenzoxy dipeptide in dioxane and the complete insolubility of the carbobenzoxy tripeptide in dioxane. We therefore slightly modified the conditions for this reaction. We took advantage of the ready solubility of carbobenzoxy peptides in aqueous alkaline solutions. The formation of simple peptide anhydrides proceeded by a mechanism similar to that for the preparation of amino acid anhydrides, i.e.:



This mechanism was checked by carrying out the preparation of carbobenzoxyglycine anhydride, previously prepared by us by performing the synthesis in dioxane. And it transpired that this replacement of dioxane by aqueous alkali not only directs the reaction in the required direction but also accelerates it. This reaction proceeds instantaneously in presence of NaOH. In addition, the working up of the reaction products is greatly simplified, and the main product (in the case of carbobenzoxyglycine anhydride) is obtained in high yield and maximum purity (carbobenzoxyglycine anhydride melts at 119° without recrystallization), whereas the m.p. after repeated recrystallization of the carbobenzoxyglycine anhydride prepared in a medium of dioxane did not exceed 114°.

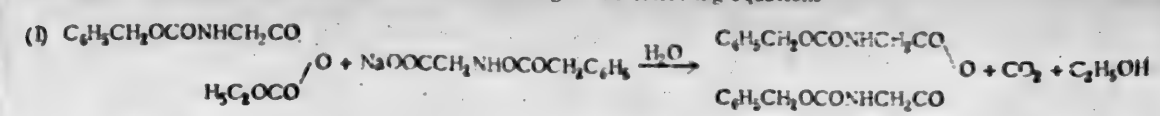
6. Preparation of carbobenzoxyglycine anhydride.* 4.18 g carbobenzoxyglycine was dissolved in 20 ml absolute dioxane and 2.4 ml isobutyldimethylamine was added. To the solution (cooled to 10°) was added 1.9 ml ethyl chloroformate and the mass was left at room temperature for 10 minutes. Addition was then made of 4.18 g carbobenzoxyglycine in 20 ml 1 N caustic alkali. After an interval of 5 minutes (to allow the frothing to subside) the precipitate was filtered, washed three times with water (to dissolve the amine hydrochloride), with alcohol (to remove unreacted carbobenzoxyglycine) and with ether. After drying in a vacuum desiccator the substance melted at 119°. Yield 6.5 g or 81% of the theoretical. Concentration of the aqueous alcoholic mother liquor yielded a further 1 g of

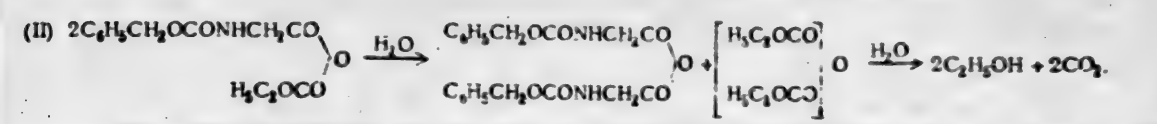
* In 1950 Wieland and co-workers obtained carbobenzoxyglycine anhydride by heating carbobenzoxyglycine acetate in benzene to 40°. This product melted at 118° after recrystallization (instead of at 119° in our reaction conditions and without recrystallization). The authors propose the following reaction mechanism:



Application of this reaction, however, to the preparation of other amino acid anhydrides did not meet with success.

substance. The reaction probably proceeds according to the following equations:





Note. When the substance with m.p. 119° was recrystallized from nitrobenzene, it had a m.p. 114°, indicating decomposition.

The following experiment showed, however, that the synthesis of carbobenzoxyglycine anhydride can take place in two stages on condition that an aqueous medium is used. 2.14 g carbobenzoxyglycine was dissolved in 10 ml absolute dioxane and 1.2 ml isobutyldimethylamine. While cooling with water, addition was made of 0.95 ml ethyl chloroformate and the mass left for 10 minutes at room temperature, after which 10 ml water was added. Violent frothing and CO_2 evolution took place for one minute. The precipitate was filtered, washed with water, and three times with alcohol. The properties of the substance and its m.p. of 119° indicated that it was carbobenzoxyglycine anhydride. Yield 0.5 g or 25% of the theoretical.

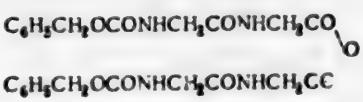
On the basis of the above facts we must regard the formation of carbobenzoxyglycine anhydride in an aqueous medium as the result of two reactions I and II (this is evidenced also by the yield of carbobenzoxyglycine anhydride which in water is 81% and in dioxane is 50%).

7. Preparation of carbobenzoxyglycylglycine anhydride. 0.66 g carbobenzoxyglycylglycine was dissolved in 10 ml absolute dioxane and 0.5 ml triethylamine. Addition was then made of 0.3 ml ethyl chloroformate, followed after an interval of 10 minutes by 0.66 g carbobenzoxyglycylglycine dissolved in 10 ml absolute dioxane and 0.5 ml triethylamine (for increasing the solubility of the carbobenzoxy dipeptide). After one hour the precipitate was filtered off and washed first with alcohol and then with ether. The substance (dried in a vacuum desiccator) melted at 146°. The substance with m.p. 146° was treated with boiling ethanol in a beaker and then filtered and washed on the filter several times with alcohol. Under the microscope the filtrate crystallizes in homogeneous needles which settle when ether is added. The alcoholic filtrate was precipitated with ether. The resultant substance was the original carbobenzoxyglycylglycine.

The precipitate which had been treated with alcohol and was insoluble in it was recrystallized from nitrobenzene. M.p. 148°.

Note. Carbobenzoxyglycylglycine is soluble in boiling dioxane, in alcohols and in hot nitrobenzene. It comes down from hot ethyl alcohol in the form of needles. The obtained substance is absolutely insoluble in alcohol. It crystallizes from nitrobenzene in characteristic semilyrate crystals.

Proposed formula:



Found %: C 56.14, 55.98; H 5.25, 5.15; N 10.85, 10.81. $C_{24}H_{26}O_9N_4$. Calculated %: C 56.03; H 5.06; N 10.89.

Determination of the acid equivalent. 0.0531 g substance: 0.05 ml 0.1 N NaOH. After standing for 24 hours the solution was acidified. Hydrolysis consumed 0.15 ml 0.1 N NaOH in the titration. Corresponding to 11.3 equivalents.

8. Preparation of the carbobenzoxy tripeptide anhydride. 0.32 g carbobenzoxy tripeptide was dissolved in 10 ml absolute dioxane and 0.2 ml triethylamine. Addition was then made of 0.11 g ethyl chloroformate. After standing for 10 minutes, addition was made to the mixture of 0.32 g carbobenzoxy tripeptide in 10 ml dioxane and 0.2 ml triethylamine. After standing for two hours, the precipitate was filtered off and washed with dioxane, alcohol (several times) and ether. The substance dried in a desiccator had m.p. 156°. In order to free the reaction product from the original carbobenzoxy tripeptide, aqueous alcohol and neutral red were added to it. It was titrated with 0.1 N NaOH and the insoluble precipitate was filtered off and washed with water and (repeatedly) with alcohol to remove the color. The insoluble precipitate was analyzed.

Proposed formula:

$$C_6H_5CH_2OCONHCH_2CONHCH_2CONHCH_2CO$$
$$\diagdown\!\diagup O$$
$$C_6H_5CH_2OCONHCH_2CONHCH_2CONHCH_2CO$$

Found %: C 52.65, 52.73 H 5.19, 5.31; N 13.30, 13.35; incombustible residue 1.71, 1.68.
$C_{28}H_{28}O_{11}N_6$. Calculated %: C 53.5; H 5.09; N 13.38.

Note: The analytical data clearly indicate that we are dealing with the anhydride of the phthaloyl tripeptide contaminated with Ba, since the incombustible residue amounts to 1.7% of the total weight. Barium was present in the titrated alkali solution. It is therefore necessary to take into consideration the separation of the carbobenzoxy tripeptide anhydride from the original carbobenzoxy tripeptide. We could probably achieve complete separation of the anhydride from the original peptide by titration with alkali, but only if barium was absent from the alkali.

II. Synthesis of Peptides with the Help of Simple Amino Acid Anhydrides.

1. Synthesis of phthaloylglycylglycine. 1 g phthaloylglycine anhydride was mixed with 0.27 g glycine in 15 ml water and 0.28 g NaOH (2 moles NaOH per mole of formed phthaloyl dipeptide and per mole of phthaloylglycine resulting from the reaction). The suspension was shaken on the machine for an hour; part of the precipitate failed to dissolve. An additional 0.1 g NaOH was then added and the whole dissolved on further shaking. At the end of the reaction the solution was neutralized with hydrochloric acid until the reaction was weakly acid, and evaporated to dryness in vacuum. The residue was taken up with water, filtered, and washed with water until the wash liquors gave a negative reaction for halogen. The precipitate then was washed three times with alcohol (phthaloylglycine was detected in the filtrate) and then with ether. The substance, dried in a vacuum desiccator, melts at 231° and gives a dipeptide biuret reaction. Analysis indicates that the substance is phthaloylglycylglycine [7]. Yield 0.35 g or 53% of the theoretical.

The reaction proceeds according to the scheme:

$$\begin{matrix} C_6H_4(CO)_2NCH_2CO \\ \diagdown\!\diagup O \\ C_6H_4(CO)_2NCH_2CO \end{matrix} + NH_2CH_2COOH \xrightarrow[H_2O]{NaOH} C_6H_4(CO)_2NCH_2COONa + C_6H_4(CO)_2NCH_2CONHCH_2COONa.$$

2. Synthesis of phthaloylglycylglycylglycylglycine. 1 g of phthaloylglycine anhydride was mixed with 0.65 g glycylglycylglycine dissolved in 15 ml water with 0.28 g NaOH. The reaction mixture was agitated on the shaker for an hour; a very small amount failed to dissolve; a further 0.05 g NaOH was therefore added. Vigorous shaking resulted in a transparent solution. After neutralization, the solution was evaporated to dryness in a vacuum. The precipitate brought on to a filter with alcohol, was insoluble in organic solvents and slightly soluble in water. After treatment with water (for removal of NaCl) the precipitate was washed with alcohol. The alcoholic filtrate proved to be entirely free from any compound.

When the biuret reaction was performed with the precipitate, a clear red color was developed in the first instant of addition of the copper solution, and only after addition of excess of copper did a violet color appear. This precipitate is inevitably a mixture of the formed phthaloyl tetrapeptide and the original tripeptide. But due to their extraordinarily similar solubility characteristics (soluble in water, insoluble in organic solvents), this mixture could not be separated into its components. However, the separation from the alcoholic filtrate (when working up the main precipitate) of phthaloylglycine clearly points to the following course of the reaction:

$$\begin{matrix} C_6H_4(CO)_2NCH_2CO \\ \diagdown\!\diagup O \\ C_6H_4(CO)_2NCH_2CO \end{matrix} + NH_2CH_2CONHCH_2CONHCH_2COONa \longrightarrow C_6H_4(CO)_2NCH_2COOH +$$
$$+ C_6H_4(CO)_2NCH_2CONHCH_2CONHCH_2CONHCH_2COOH$$

It was consequently impossible to isolate the phthaloyl tetrapeptide from this reaction. We only established its undoubted formation from the evidence of the red biuret reaction.

3. Synthesis of carbobenzoxyglycylglycine. 0.37 g glycine was dissolved in 10 ml (2 moles) 1 N NaOH and 2 g carbobenzoxyglycine anhydride was added. After 15 minutes' standing the perfectly transparent solution

was acidified with hydrochloric acid. The resultant precipitate was filtered off and washed first with water and then with alcohol (3 times)(for separation from carbobenzoxyglycine) and ether. After drying in a vacuum desiccator, the substance melted at 178°, its other properties (positive biuret reaction of the dipeptide type, insolubility in water and poor solubility in alcohol) identified it with carbobenzoxyglycylglycine [6]. Yield 1.0 g or 75% of the theoretical.

Formation of carbobenzoxyglycylglycine proceeds according to the following scheme:

$$C_6H_5CH_2OCONHCH_2CO\!\!\!

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Received July 7, 1952

ORGANIC INSECTOFUNGICIDES

XII SYNTHESIS OF MIXED ESTERS OF PHOSPHORIC AND THIOPHOSPHORIC ACID

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Several esters of phosphoric and thiophosphoric acids have found quite extensive application in agriculture as destroyers of various plant pests [1-14]. Diethyl-4-nitrophenylthiophosphate has found particularly extensive application, its destructive action considerably surpassing that of such active substances as DDT, hexachlorocyclohexane, nicotine and anabasine. This group of compounds has consequently attracted the interest of many investigators and at the present time several hundred derivatives of phosphoric and thiophosphoric acid have been studied for their action on plant pests; the number of compounds synthesized and studied in this field continually increases. But notwithstanding the great number of publications in this field there is an absence from the literature of systematic studies of the dependence of the activity of organic compounds of phosphorus in relation to plant pests on their structure.

In view of the great interest in this group of compounds, we undertook an investigation of the synthesis of various esters of phosphoric and thiophosphoric acids with the aim of studying the relation between the intensity of their action on plant pests and their structure.

In the first place we synthesized and studied the esters of phosphoric and thiophosphoric acids with the general formulas (I) and (II):

$$C_6H_n\left[OP(O)(OR)_2\right]_n \quad (I) \qquad C_6H_n\left[OP(S)(OR)_2\right]_n \quad (II)$$

Esters of phosphoric acid were synthesized by the general reaction applied to the preparation of compounds of this type [15]:

$$PCl_3 \rightarrow (RO)_2POH \rightarrow (RO)_2P(O)Cl \rightarrow C_6H_n\left[OP(O)(OR)_2\right]_n$$

Mixed esters of thiophosphoric acid were similarly prepared according to the following general schemes [16, 17]:

$$ROH + PSCl_3 \longrightarrow (RO)_2PSCl + HCl \qquad 2(RO)_2PSCl + C_6H_4(ONa)_2 \longrightarrow C_6H_4\left[OP(S)(OR)_2\right]_2 + 2NaCl$$

The compounds that we prepared and their properties are set out in Tables 1 and 2, and their activity toward the grain weevil (Calandra granaria) is detailed in Table 3. The pesticidal tests were carried out by P.V. Popov.

From the data of Table 3 we see that the phosphoric acid esters are more active than the thiophosphoric acid esters. The activity of phosphoric acid esters increases with increasing molecular weight of the aliphatic hydrocarbon radical, while that of the thiophosphoric acid esters decreases. Hydroquinone derivatives are rather more active than resorcinol derivatives.

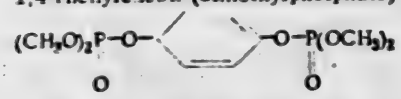
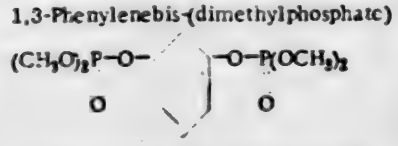
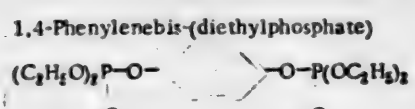
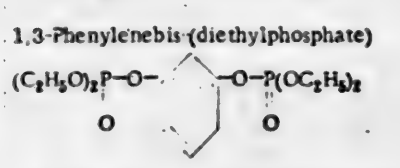
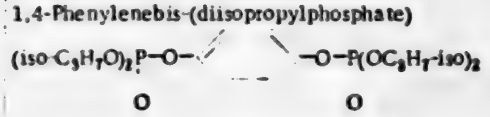
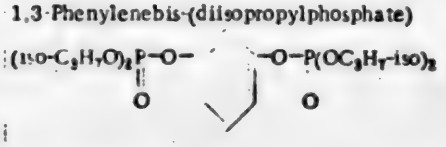
EXPERIMENTAL

Preparation of mixed esters of phosphoric acid. Into a flask fitted with a reflux condenser and a stirrer we introduced 1 mole of the phenol, 2 moles dialkylchlorophosphate, 4-8 times the weight of acetone and 2-3 moles anhydrous sodium carbonate in fine powder form. The mixture was boiled with thorough stirring for 4-6 hours. At the conclusion of the reaction the formed NaCl, $NaHCO_3$ and the excess of sodium carbonate were filtered off, the acetone was distilled off from the filtrate and the residue was fractionated in vacuum. The compounds so prepared are listed in Table 1. Phosphorous determinations on all the compounds were carried out by the photocolorimetric method.

Preparation of mixed esters of thiophosphoric acid. We employed Toy's [18] method in slightly modified form. Into a four-necked flask fitted with a stirrer, dropping funnel, thermometer and reflux condenser was introduced the phenol to which had been added an equimolecular amount of sodium methylate. The methyl alcohol was distilled off and to the dry residue was added chlorobenzene and the appropriate dialkylchlorothiophosphate

TABLE 1

Properties of Phosphoric Acid Esters

Prep. No.	Name and formula	B.p.	d_4^{20}	n_D^{20}	Yield (%)	Analysis for P (%) found	calc.
1	1,4-Phenylenebis-(dimethylphosphate) 	95-98° at 0.02 mm	1.3883	1.4738	70	18.65, 18.72	19.02
2	1,3-Phenylenebis-(dimethylphosphate) 	110-115 at 0.025 mm	1.2720	1.4997	31	18.75, 18.82	19.02
3	1,4-Phenylenebis-(diethylphosphate) 	118-121 at 0.15 mm	1.1913	1.4575	61	15.95, 16.32	16.02
4	1,3-Phenylenebis-(diethylphosphate) 	155-156 at 0.13 mm	1.2048	1.4856	39	15.87, 15.93	16.02
5	1,4-Phenylenebis-(diisopropylphosphate) 	102-110 at 0.024 mm	1.2250	1.4440	78.5	14.01, 13.97	14.15
6	1,3-Phenylenebis-(diisopropylphosphate) 	110-112 at 0.035 mm	1.1069	1.4500	78.7	13.8, 13.98	14.15

A few drops of pyridine were added as catalyst and the reaction mixture was heated with good stirring to 120-130° for 7-15 hours. At the end of the reaction the separate sodium chloride was filtered off. The chlorobenzene was distilled off from the filtrate in vacuum and the residue was washed with water, dried with calcium chloride and distilled in vacuum. The compounds that we prepared and their properties are presented in Table 2.

SUMMARY

1. 12 mixed esters of phosphoric and thiophosphoric acids were synthesized.

2. An examination of the activity of the synthesized esters toward the grain weevil showed that phosphoric acid esters are more active than thiophosphoric acid esters. Hydroquinone derivatives are more active than resorcinol derivatives.

The activity of phosphoric acid esters rises with increasing molecular weight of the aliphatic hydrocarbon radical. All the synthesized esters were less active than diethyl-4-nitrophenylthiophosphate.

TABLE 2

Properties of Thiophosphoric Acid Esters

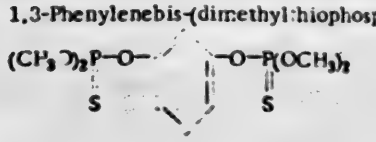
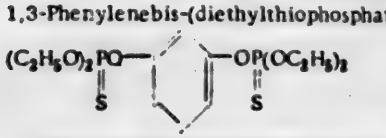
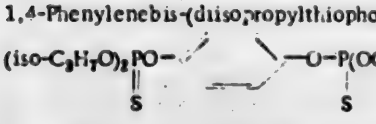
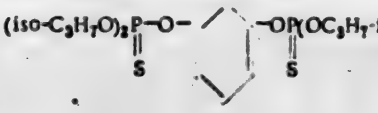
Prep. No.	Name and formula	B.p.	d_4^{20}	n_D^{20}	Yield (%)	Analysis for P (%) found	calc.
1	1,4-Phenylenebis-(dimethylthiophosphate)	105° at 0.04 mm	1.2428	1.5230	29	17.1, 17.0	17.32
2	1,3-Phenylenebis-(dimethylthiophosphate) 	120-125 at 0.16 mm	1.2890	1.5310	71	17.00, 16.95	17.32
3	1,4-Phenylenebis-(diethylthiophosphate)	134 at 0.2 mm	1.2496	1.5158	28	14.72, 14.74	14.95
4	1,3-Phenylenebis-(diethylthiophosphate) 	130 at 0.15 mm	1.1991	1.5113	51.5	14.63, 14.69	14.95
5	1,4-Phenylenebis-(diisopropylthiophosphate) 	Does not distil at 0.05 mm without decomp.	1.1720	1.5193	58.0	13.4, 13.32	13.2
6	1,3-Phenylenebis-(diisopropylthiophosphate) 	Ditto	1.1352	1.5103	33.4	12.95, 13.06	13.2

TABLE 3

Activity of Esters of Phosphoric and Thiophosphoric Acids toward the Grain Weevil.

Prep. No.	Name	Maximum concentration of preparation giving 100% kill of grain weevil in 24 hours multiplied by 10^3 (in %)
1	1,4-Phenylenebis-(dimethylphosphate)	50-100
2	1,3-Phenylenebis-(dimethylphosphate)	Over 100
3	1,4-Phenylenebis-(diethylphosphate)	25-50
4	1,3-Phenylenebis-(diethylphosphate)	Over 100
5	1,4-Phenylenebis-(diisopropylphosphate)	5-25
6	1,3-Phenylenebis-(diisopropylphosphate)	5-25
7	1,4-Phenylenebis-(dimethylthiophosphate)	100-250
8	1,3-Phenylenebis-(dimethylthiophosphate)	Over 1000
9	1,4-Phenylenebis-(diethylthiophosphate)	1000
10	1,3-Phenylenebis-(diethylthiophosphate)	100
11	1,4-Phenylenebis-(diisopropylthiophosphate)	1000
12	1,3-Phenylenebis-(diisopropylthiophosphate)	1000
13	Diethyl-4-nitrophenylthiophosphate	2.5-5

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Received July 6, 1952

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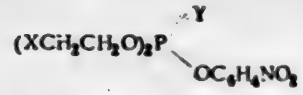
XIII. SYNTHESIS OF MIXED ESTERS OF PHOSPHORIC AND THIOPHOSPHORIC ACIDS CONTAINING THE SIMPLEST SUBSTITUENTS IN THE ALIPHATIC RADICAL

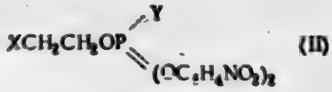
M. L. Galashina, I. L. Vladimirova, Ya. A. Mandelbaum and N. N. Melnikov

It was recently shown [1] that dialkynitrophenylthiophosphates are fairly active insecticides, while diethyl-4-nitrophenylthiophosphate has found practical application in agriculture [2-10]. We also know that the position and character of the substituent in the aromatic radical very profoundly influence the insecticidal activity of a compound. In this connection it was of interest to synthesize and study mixed esters of phosphoric and thiophosphoric acids containing the simplest possible substituents in the aliphatic radical and a nitrogroup in the aromatic radical.

In the first instance we synthesized compounds with the general formulas (I) and (II):



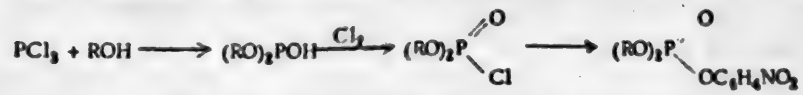
(I)

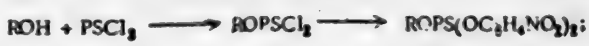


(II)

where X is chlorine or C_2H_5O and Y is oxygen or sulfur.

These compounds were synthesized by the general reaction for this type of compound.





A list of the synthesized compounds and their properties appears in Table 1.

TABLE 1

Name and formula	M.p.	d_4^{20}	n_D^{20}	Analysis for P (%)	
				found	calculated
β-Chloroethyl-4,4'-dinitrodiphenylphosphate $ClCH_2CH_2OPO(OC_6H_4NO_2)_2$	86-87°	–	–	7.24, 7.46	7.70
β-Chloroethyl-4,4'-dinitrodiphenylthiophosphate $ClCH_2CH_2OPS(OC_6H_4NO_2)_2$	95-96	–	–	7.50, 7.60	7.40
β,β'-Dichloroethyl-4-nitrophenylthiophosphate $(ClCH_2CH_2O)_2PSOC_6H_4NO_2$	Does not distil at 0.02 mm	–	1.5780	8.00, 8.21	8.61
β-Ethoxyethyl-4'-dinitrodiphenylphosphate $C_2H_5OCH_2CH_2OPO(OC_6H_4NO_2)_2$	72-73	–	–	7.50, 7.42	7.53
β-Ethoxyethyl-4,4'-dinitrodiphenylthiophosphate $C_2H_5OCH_2CH_2OPS(OC_6H_4NO_2)_2$	75-76	–	–	7.3, 7.22	7.23
β,β'-Diethoxydiethyl-4-nitrophenylphosphate $(C_2H_5OCH_2CH_2O)_2PO(OC_6H_4NO_2)$	–	1.2720	1.5050	8.32, 8.20	8.5

TABLE 2

Name and formula	M.p.	d_4^{20}	n_D^{20}	Analysis for P (%) found	Analysis for P (%) calculated	Yield (%)
β-Chloroethyldichlorothiophosphate $ClCH_2CH_2OPSCl_2$	104-108° at 14 mm	1.4671	1.5362	14.65, 14.71	14.52	44
β,β'-Dichlorodiethylchlorothiophosphate $(ClCH_2CH_2O)_2PSCl$	130 at 17 mm	1.5135	1.5641	11.85, 11.78	12.05	24
β,β',β''-Trichlorotriethylthiophosphate $(ClCH_2CH_2O)_3PS$	142-150 at 9 mm	1.4778	1.5650	10.12, 10.10	10.20	30
β-Ethoxyethyldichlorothiophosphate $C_2H_5OCH_2CH_2OPSCl_2$	108-114 at 23 mm	1.294	1.4910	13.4, 13.3	13.68	32
β-Ethoxyethyldichlorophosphate $C_2H_5OCH_2CH_2OPOCl_2$	110-114 at 21 mm	1.317	1.4452	14.5, 14.8	14.96	44
β,β'-Diethoxydiethylchlorophosphate $(C_2H_5OCH_2CH_2O)_2POCl$	154 at 7 mm	1.152	1.4310	11.52, 11.63	11.8	85

Tests of the synthesized compounds on the grain weevil (Calandra Granaria), carried out by P. V. Popov, showed that the whole of this group of compounds is less active than diethyl-4-nitrophenylthiophosphate.

EXPERIMENTAL

1. Preparation of alkylchlorothiophosphates. We prepared alkylchlorothiophosphates by reacting the appropriate alcohol with thiophosphorylchloride in presence of pyridine [11]. For example, β,β'-dichlorodiethylchlorothiophosphate was prepared in the following conditions: To 37.6 g $PSCl_3$ in 70 ml dry dichloroethane at −2° and with good stirring was added gradually a solution of 32 g ethylene chlorohydrin and 32 g pyridine in 32 ml dichloroethane. At the end of the addition of the specified amount of ethylene chlorohydrin and pyridine, the reaction mixture was stirred for 3 hours at 5-10°. Later the reaction mixture was treated with ice water for removal of pyridine hydrochloride. The dichloroethane solution was dried with sodium sulfate and after distillation of the dichloroethane (in vacuum) the residue was distilled in vacuum. Yield 9 g (24%).

Other esters of chlorothiophosphoric acid were similarly prepared. The properties of the prepared compounds are presented in Table 2. Esters of dichlorophosphoric acid were prepared by reaction of the corresponding alcohol with phosphorus oxychloride.

2. Preparation of mixed esters of phosphoric and thiophosphoric acids. Mixed esters of thiophosphoric acid were synthesized by a slightly modified Toy procedure [12], involving reaction of esters of chlorothiophosphoric acid with dry p-nitrophenylphenate in chlorobenzene solution with pyridine as catalyst. Into a flask fitted with a stirrer, a reflux condenser and a thermometer was introduced the phenol to which was added an equimolar amount of sodium methylate. The methyl alcohol was evaporated off and to the dry residue was added chlorobenzene, the dialkylchlorothiophosphate and pyridine. The reaction mixture was kept at 130° for 5-7 hours. While cooling, the sodium chloride was filtered off; the chlorobenzene was distilled off in vacuum, and the residue was washed with water, dried and fractionated in vacuum. The compounds that we prepared are listed in Table 1. Of these compounds, only β,β'-dichlorodiethyl-4-nitrophenylthiophosphate has been described in a U.S. patent [13], while the others have not been described in the literature. The ester described in the U.S. patent had been prepared by an entirely different method.

SUMMARY

A series of mixed esters of phosphoric and thiophosphoric acids containing chlorine and ethoxyl in the aliphatic radical were synthesized and their properties examined. Of the compounds synthesized, not one exhibited greater activity as an insecticide than diethyl-4-nitrophenylthiophosphate.

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Received July 6, 1952

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FREE RADICALS IN THE DECOMPOSITION REACTIONS OF BENZYLAMINODIAZOBENZENE IN SOLVENTS

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Very great interest has been aroused in recent years by azo and diazo compounds which decompose by a radical mechanism at relatively low temperatures [1]. Thus the azodinitriles and esters of azodicarboyxlic acids have been closely studied.

These compounds are good initiators of polymerization processes and possess a number of advantages over other agents in use for technical purposes, e.g. peroxides [2].

It is known that diazoaminobenzene can also be used as an initiator of polymerization of some vinyl derivatives, for example acrylonitrile in block form and butadiene in aqueous emulsion [3]. It acts as a slower (relative to benzoyl peroxide) but more continuous source of free radicals.

The mechanism of decomposition of azo compounds of the type of azodinitriles and esters of azodicarboxylic acids has been analyzed in the literature, but no data have been published about diazoamines. We therefore considered it of interest to study this process with reference to benzylaminodiazobenzene (I).

In the literature [4] this compound is described a yellow crystalline substance with m.p. 73°, capable of rearrangement to the tautomeric form (II) in presence of acids:

$$C_6H_5CH_2NH{-}N{=}N{-}C_6H_5 \rightleftarrows C_6H_5CH_2N{=}N{-}NHC_6H_5$$

Our investigations revealed that this compound is less stable than diazoaminobenzene. Thermal decomposition of the dry substance starts at 95° and is accompanied by steady evolution of gas (the yield of nitrogen is 91.5% calculated on the number of evolved nitrogen molecules). In solvents (benzene, ethylene glycol monoethyl ether) vigorous decomposition starts at as low as 40-50° (nitrogen yield 90%). We refrained from attempting to purify the compound by recrystallization (due to its instability), but we usually treated its acetone solution with animal charcoal, filtered, and precipitated the benzylaminodiazobenzene with water. After cautious drying the substance melted at 72-74°.

On the basis of the quantitative yield of nitrogen evolved during decomposition in solvents, it was suggested that decomposition of this compound can proceed in two directions: by a radical mechanism with formation of phenyl and benzylamino radicals and by an intramolecular mechanism with formation of benzylaniline.

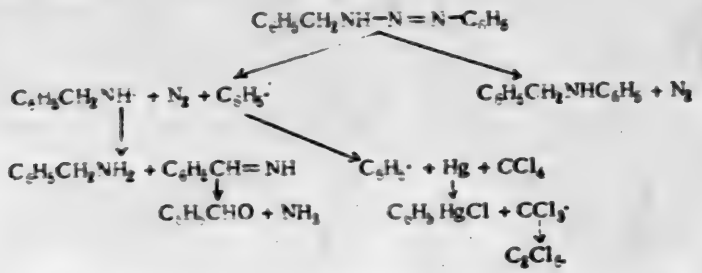
We succeeded in establishing that both these processes take place probably simultaneously. It is true that neither of them can yet be accurately characterized, due to the difficulty of quantitative separation of the reaction products. The presence of benzylaniline could be demonstrated in all cases without particular difficulty. For the identification of the phenyl radical we made use of the method of fixation on mercury, frequently used in our laboratory.

For example, Razuvaev [5] established the release of the phenyl radical from benzoyl peroxide in carbon tetrachloride through the formation of phenyl mercury chloride. Again, Razuvaev and Fedotova [6] succeeded in binding the phenyl radical to mercury when benzeneazotriphenylmethane decomposed in carbon tetrachloride.

When benzylaminodiazobenzene was decomposed in similar conditions (in carbon tetrachloride in presence of mercury) a considerable amount of phenylmercury chloride could be isolated from the reaction mixture, thereby convincingly demonstrating the formation of the phenyl radical. The participation in this process of the solvent – carbon tetrachloride – was also confirmed by the isolation of hexachloroethane from the reaction mixture.

Benzaldehyde and benzylamine were detected in considerable amounts among the products of decomposition of benzylaminodiazobenzene in carbon tetrachloride in presence of mercury, as well as in ethylene glycol monoethyl ether. It is highly probable that the formation of these substances is associated with the benzylamino radical which

by disproportionation is transformed into [illegible]lamine and benzylimine. In the process of separation of the latter, it is hydrolyzed to benzaldehyde. Con[illegible] the breakdown of benzylaminodiazobenzene in carbon tetrachloride in presence of mercury may be [illegible]ed by the following probable scheme:



Radical decomposition of benzylaminodiazobenzene in solvents was indirectly confirmed by the formation of acetaldehyde (in ethylene glycol monoethyl ether) due to splitting-off by the phenyl radical of hydrogen from the solvent (benzene could not be identified), as well as by formation of small amounts of diphenyl in exploratory experiments in benzene.

EXPERIMENTAL

1. Decomposition of Benzylaminodiazobenzene in Carbon Tetrachloride in Presence of Mercury

A solution of 6.6 g benzylaminodiazobenzene in 25 ml carbon tetrachloride in presence of 50 g metallic mercury was heated on a water bath with vigorous stirring for 7 hours. Completion of the reaction was signalized by cessation of evolution of nitrogen. The contents of the reaction flask were carefully decanted from the mercury, acidified with hydrochloric acid (for binding of amines) and steam-distilled. Carbon tetrachloride collected in the receiver together with a small amount of oily liquid with the characteristic odor of benzaldehyde. The carbon tetrachloride was separated from the aqueous layer, dried and distilled. Hexachloroethane crystallized from the residue. It was separated from the small amount of liquid fraction. Its weight was 0.5 g (7% of theory); m.p. 186° in a sealed capillary; m.p. of its mixture with a pure specimen in a sealed capillary was 186°. After separation of the crystals of hexachloroethane, the liquid was combined with the ether extracts from the aqueous layer and fractionated. A fraction boiling at 176-182° was isolated in the amount of 1.2 g (34.3% of theory) and tested for the presence of the carbonyl group. The following were prepared:

Dimedone derivative with m.p. 196° (according to the literature the dimedone derivative of benzaldehyde melts at 196°). A mixture with a pure specimen melts at 195°. 2,4 Dinitrophenylhydrazone with m.p. 235° (237° in the literature); a mixture with a pure sample melts at 237°. A silver mirror was formed with ammoniacal mercuric oxide. The presence of benzaldehyde was thus definitely confirmed.

After distilling off the carbon tetrachloride and the benzaldehyde, the liquid remaining in the flask was made alkaline and again steam-distilled. At the end of the distillation, the flask contained a resinous residue (A). The condensate was extracted with ether, dried and fractionated to give a benzylamine fraction of 0.5 g, boiling at 182° (yield 15% of theory) and a benzylaniline fraction of 1.3 g (19.5%) boiling at 302°. The benzylamine was identified by formation of benzylphthalimide with m.p. 115° (literature 116°) (a mixed sample melts at 115°) and by formation of a crystalline derivative with ethyl acetate melting at 60° (literature 61°; mixed m.p. 60°). Benzylaniline was identified as the nitrosamine by Liebermann's reaction [7] and from the m.p. of the hydrochloride (222° compared with the literature value of 224°). The molecular weight of the salt was determined by titration with alkali in presence of phenolphthalein. Found: M 222.6. $C_{13}H_{14}Cl$. Calculated: M 219.5.

The mercury and the resinous substance (A) were repeatedly treated with hot acetone. After cooling, the acetone deposited crystals of phenylmercuric chloride in the amount of 1.5 g with m.p. 256° (literature 258°; mixed m.p. 257°). The yield of phenylmercuric chloride is 15.7% of theory.

2. Decomposition of Benzylaminodiazobenzene in Ethylene Glycol Monoethyl Ether

A solution of 2.5 g benzylamino diazobenzene in 20 ml ethylene glycol monoethyl ether was heated first on the water bath and then on a metal bath until nitrogen ceased to come off. The reaction mixture was acidified and steam-distilled. The condensate was extracted with ether, the ether extract was dried and fractionated.

Fractionation gave 0.35 g benzaldehyde (31.5% of theory). From this fraction was prepared the dimedone derivative of benzaldehyde with m p. 196°, also the 2,4-dinitrophenylhydrazone with m.p. 235°. The residue in the reaction flask was made alkaline and again steam-distilled. The condensate was extracted with ether, the ether extract was dried and the ether driven off. The benzylamine in the residue was separated from the benzylaniline by treatment with phthalic anhydride 0 23 g benzylphthalimide with m.p. 115° (literature 116°) was isolated. On the basis of benzylamine the yield was 0.1 g (10% of theory). 0.5 g (20% of theory) benzylaniline was isolated and identified in the form of the nitrosamine by Liebermann's reaction and by the m.p. of the hydrochloride (220°). In the aqueous solution, after steam distillation, was found acetaldehyde, identified as the dimedone derivative with m p. 140° (literature 140°; mixture with the pure substance melts at 140°), and as the 2,4-dinitrophenylhydrazone with m.p. 160-168° (literature 168°). The mixed melting point was 167°. The acetaldehyde was not quantitatively determined. Benzene could not be detected among the reaction products.

SUMMARY

1. The decomposition of benzylaminodiazobenzene in ethylene glycol monoethyl ether and carbon tetrachloride in presence of mercury was studied Benzaldehyde, benzylamine, benzylaniline and acetaldehyde were separated from the products of reaction in ethylene glycol monoethyl ether. Phenylmercuric chloride, benzaldehyde, benzylamine and benzylaniline were separated from the products of reaction in carbon tetrachloride.

2. The composition of the reaction products indicated that two processes proceed simultaneously—a radical process (with formation of phenyl and benzylamino radicals) and an intramolecular process (with formation of the secondary amine, benzylaniline).

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Received July 8, 1952

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THE PROBLEM OF THE MECHANISM OF FORMATION OF 2-SUBSTITUTED OXAZOLONES

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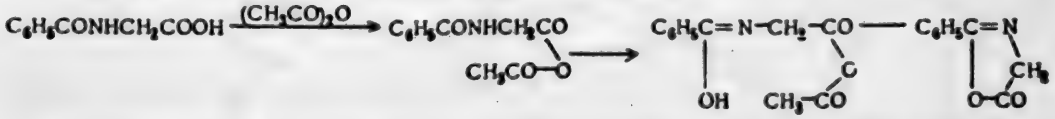
It is known that 2-phenyl-5-oxazolone is readily formed by reaction of hippuric acid with acetic anhydride [1]. The yield of oxazolone can be raised from 49 to 64% by treating hippuric acid with a large excess of acetic anhydride at 15-20°.

All attempts to prepare 2-benzyl-5-oxazolone from phenaceturic acid have proved unsuccessful. Many investigators [2] have tried to demonstrate its presence in the reaction mass by preparing derivatives; for example, treatment with ammonia and benzylamine gave the amide and benzylamide of phenaceturic acid; this method, however, cannot serve as evidence of the formation of 2-benzyl-5-oxazolone. Indeed, the action on phenaceturic acid of various dehydrating agents such as acetic anhydride, phosphorus tribromide, etc. may be expected to lead to formation of the mixed anhydride of phenaceturic and acetic acids or the anhydride of phenaceturic acid. When these compounds are treated with ammonia or benzylamine they will give the same substances as are formed by 2-benzyl-5-oxazolone.

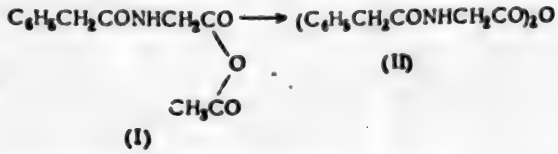
In this investigation an attempt has been made to study the mechanism of the reaction between phenaceturic acid and acetic anhydride and to ascertain why 2-benzyl-5-oxazolone is not formed.

In all probability the process of formation of 2-phenyl-5-oxazolone from hippuric acid and acetic anhydride proceeds through the stage of the mixed anhydride of hippuric and acetic acids with simultaneous tautomerization of the amido bond and closure of the oxazolone ring.



The susceptibility of the amido bond to tautomeric transformation is an indispensable condition for formation of the oxazolone ring. It is very probable that different acylamino acids differ from one another in susceptibility to tautomeric change of the amido bond and that they are capable to a greater or lesser extent of changing into oxazolones in dependence on the structure of the amino acid and of the acylating carboxylic acid. We know that not only hippuric acid but also many of its derivatives readily change into oxazolones [3]. When the tautomerism of the acylamino acids is weakly developed, the oxazolone is formed in such small amount that it does not appear possible to isolate it in the pure form.

Phenaceturic acid may be regarded as belonging to this type of acylamino acids. When reacted with acetic anhydride, it apparently first forms the mixed anhydride of phenaceturic and acetic acids (I), which dissolves in excess acetic anhydride. In the course of removal of the acetic anhydride, the equilibrium is shifted in the direction of formation of phenaceturic anhydride (II) which quickly crystallizes at the conclusion of the distillation:



(I)

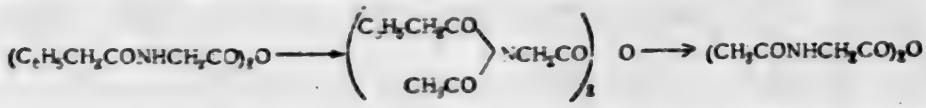
Compound (II) usually contains a small amount of the anhydride of N-acetylphenaceturic acid which is removed by recrystallization from acetone.

After filtration of phenaceturic anhydride, the mother liquor is concentrated in vacuum and left to crystallize. After a few days the anhydride of N-acetylphenaceturic acid comes down. The non-susceptibility to tautomerism of the amide bond in phenaceturic anhydride prevents it from undergoing transformation into 2-benzyl-5-oxazolone Phenaceturic anhydride very readily enters into reaction with acetic anhydride, forming N-acetylphenaceturic anhydride The reaction takes place even in the cold, and this may be accounted for by the great lability of the hydrogen of the amido group

Under the action of ammonia N acetylphenaceturic anhydride breaks down to phenylacetamide, the amide of aceturic acid, and aceturic acid (the latter was not isolated from the mother liquors). The action of sodium hydroxide solution on N-acetylphenaceturic acid leads to salts of aceturic and phenylacetic acids.

The above reactions justify the assumption that the phenacetyl residue in N acetylphenaceturic acid is less firmly attached to the amido group than is the acetyl residue.

In the preparation of various oxazolones by Erlenmeyer's method from phenaceturic, caproylaminoacetic and other acids, transacylation readily occurs of the acylamino acids [4]. On the basis of the foregoing facts, it follows that the transacylation reaction proceeds through the stage of formation of intermediate mixed diacylamino acids which in the course of further reaction readily lose one acylating group.



Hippuric acid evidently readily gives the tautomeric form of the amido bond and is therefore incapable of forming diacylamino acids but is at once converted into 2-phenyl-5-oxazolone.

EXPERIMENTAL

2-Phenyl-5-oxazolone. 30 g hippuric acid was mixed with 350 g acetic anhydride at 20° for 8 hours. The residual hippuric acid (13.6 g) was filtered off and dried.

The filtrate was concentrated on a water bath at 40° in vacuum. The residual orange oil crystallized. The azlactone was extracted from this mass with petroleum ether three times (100 ml each time) at 60-70°. Cooling of the solution to 0° led to separation of large, lustrous, orange plates. Yield 12 g or 64%. The azlactone was recrystallized from absolute ethyl alcohol (1:3). Yellow plates with m.p. 90-92° (1).

Phenaceturic anhydride. 30 g phenaceturic acid and 300 g acetic anhydride were mixed at 15-20° for 4 hours until the precipitate had almost completely dissolved. A minute amount (0.5 g) phenaceturic acid was filtered off and acetic acid and excess acetic anhydride were distilled off from the filtrate in vacuum at 40-45° on a water bath. At the close of the distillation the mass in the flask crystallized. On the following day the crystal mass was well stirred with 100 ml absolute ether and the insoluble white crystalline material was filtered off, washed with absolute ether and recrystallized from dry acetone. White, finely crystalline precipitate with m.p. 108-109°. Yield 17 g.

3.740 mg substance: 8.841 mg CO_2; 1.815 mg H_2O. 3.737 mg substance: 8.871 mg CO_2; 1.919 mg H_2O. 5.104 mg substance: 0.338 ml N_2 (21°, 732 mm). 5.670 mg substance: 0.374 ml N_2 (21°, 732 mm). 0.1768 g substance: 2.05 ml 0.5 N NaOH (back titration) 0.2510 g substance: 2.9 ml 0.5 N NaOH. Found %: C 64.51, 64.78; H 5.43, 5.74; N 7.4, 7.37. Anhydride groups: 20.87, 20.79. $C_{22}H_{22}O_5N_2$. Calculated %: C 65.16; H 5.48, N 7.00; anhydride groups 19.57.

Heat was developed when 1 g of the substance was dissolved in 10 ml concentrated ammonia and on the following day a precipitate of the amide of phenaceturic acid came down with m.p. 174-175°.

Hydrolysis of 1 g anhydride with 10 ml 5% sodium hydroxide solution followed by acidification with hydrochloric acid solution led to separation of phenaceturic acid with m.p. 143°.

N Acetylphenaceturic anhydride. The ether was distilled off in vacuum from the mother liquor following filtration of phenaceturic anhydride, leaving a thick, brown oil which gradually crystallized. After several days the crystals were filtered, washed with dry ether and recrystallized from dry acetone. White crystals with m.p. 175-176°.

6.870 mg substance: 0.372 ml N_2 (22°, 736 mm). 6.783 mg substance: 0.357 ml N_2 (20.5°, 741 mm). Found %: N 6.07, 5.99. $C_{14}H_{14}O_5N_2$. Calculated %: N 6.17.

Cleavage of N acetylphenaceturic anhydride with aqueous ammonia. 4.5 g of the substance was treated with 50 ml ammonia; heat was developed. On the following day the precipitate was filtered and dried at 60°. M.p. 156° (after recrystallization from water). It was identified as the amide of phenylacetic acid by the absence of depression in the mixed melting point determination. Yield 2.4 g.

The solution after filtration of the phenylacetamide was evaporated to dryness in vacuum on a water bath. The crystalline residue was dissolved in 8 ml ethyl alcohol. Rapid separation occurred of large white prisms which were recrystallized from 5 ml alcohol. M.p. 135-137° [5].

3.521 mg substance: 5.379 mg CO_2; 2.250 mg H_2O. 4.001 mg substance: 6.090 mg CO_2; 2.440 mg H_2O. 6.772 mg substance: 11.8 ml 0.01 N H_2SO_4. 4.344 mg substance: 7.65 ml 0.01 N H_2SO_4 (Kjeldahl). Found %: C 41.69, 41.54; H 7.15, 6.82; N 24.4, 24.66. $C_4H_8O_2N_2$. Calculated %: C 41.36; H 6.94; N 24.12.

This compound was identified as aceturic acid amide.

Cleavage of N-acetylphenaceturic anhydride by sodium hydroxide solution. 6.3 g anhydride was mixed with 20 ml water and gradual addition was made of 13 ml 15% sodium hydroxide solution. The precipitate rapidly dissolved with development of heat. On the next day the solution was made neutral, treated with carbon, filtered and acidified with concentrated hydrochloric acid. Lustrous scaly crystals came down. These were filtered and recrystallized from water. M.p. 76°. They were identified by the absence of depression in the mixed m.p. determination with phenylacetic acid. Yield 2.8 g.

After separation of the phenylacetic acid, the filtrate was evaporated to dryness in vacuum on the water bath, and the resultant white crystalline mass was treated with 5 ml cold water. The insoluble portion was filtered off, washed with ether for removal of the phenylacetic acid and twice recrystallized from a little water. Dried at 100°, the compound melted at 207-208°. No m.p. depression with aceturic acid [6].

SUMMARY

Acetic anhydride reacts with phenaceturic acid to give phenaceturic anhydride and N-acetylphenaceturic anhydride. When treated with ammonia, the N-acetyl derivative breaks down to phenylacetamide and the amide of aceturic acid; hydrolysis with caustic alkali gives phenylacetic and aceturic acids.

It is suggested that the absence of tautomerism from the amido bond of phenylaceturic acid is the cause of its inability to form 2-benzyl-5-oxazolone.

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Received October 3, 1952

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THIOSEMICARBAZONES OF BENZOPHENONE AND OF SOME OF ITS DERIVATIVES. II*

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Thiosemicarbazones of aldehydes have recently acquired great interest due to the antitubercular activity exhibited by some of them [1]. Regarding benzophenone as benzaldehyde in which the benzaldehydic hydrogen is replaced by the phenyl radical, it appeared to us of interest to prepare a series of thiosemicarbazones of benzophenone and its derivatives for assay of their tuberculostatic activity in comparison with the thiosemicarbazones of benzaldehyde and its derivatives. Consequently we prepared the thiosemicarbazones of the following compounds with the general formula $RC_6H_4COC_6H_4R_1$:

1) Benzophenone (R and R_1 = H); 2) p-methoxybenzophenone (R = H, R_1 = OCH_3); 3) p-hydroxybenzophenone (R = H, R_1 = OH); 4) p-nitrobenzophenone (R = H, R_1 = NO_2); 5) p-aminobenzophenone (R = H, R_1 = NH_2); 6) p-acetaminobenzophenone (R = H, R_1 = $NHCOCH_3$); 7) p,p'-dinitrobenzophenone (R and R_1 = NO_2); 8) p,p'-diaminobenzophenone (R and R_1 = NH_2).

The general method for their preparation consists in heating an alcoholic solution of the ketone with thiosemicarbazide, the alcohol being boiled for a period of 2-6 hours. It was sometimes necessary to add one to two drops of hydrochloric acid or to use thiosemicarbazide hydrochloride instead of the base. The use of such media, however, in presence of readily saponifiable N- and O-acetyl groups led to partial saponification of these groups and it was not possible to obtain the pure thiosemicarbazones from acetoxy-, p-diacetamino- and p,p'-diacetaminobenzophenone. In these cases we obtained a mixture of substances with a content of partially deacetylated products.

The Friedel-Crafts reaction was employed for the most part in the preparation of the initial p-substituted benzophenones.

The prepared thiosemicarbazones were examined by O. O. Makeeva of the chemotherapeutic department of our institute. It was established that their antitubercular activity in vitro was very insignificant in relation to that of thiosemicarbazones of aldehydes.

EXPERIMENTAL

1. Benzophenone was prepared by the Friedel-Crafts reaction by condensation of benzene with benzoyl chloride in presence of aluminum chloride. The thiosemicarbazone was prepared by adding 1 g finely pulverized thiosemicarbazide to 2 g of benzophenone dissolved in 25 ml alcohol. The mixture was heated at 80° with good stirring for 4 hours. After cooling, the solution deposited lustrous white crystals (2.5 g). They were washed with hot water and recrystallized from alcohol. M.p. 170-171°. Yield 2.3 g (82% of the theoretical). The substance is insoluble in water, slightly soluble in cold alcohol.

Found %: N 16.30; S 12.58. $C_{14}H_{13}N_3S$. Calculated %: N 16.47; S 12.55.

2. p-Methoxybenzophenone [2]. To a mixture of 40 g anisole, 56 g benzoyl chloride and 100 ml carbon bisulfide was gradually added, with stirring, 80 g aluminum chloride. 2 hours after the addition of the whole of the aluminum chloride, the reaction mass was warmed up to 40-45° for 2 hours and left overnight. The next morning the carbon bisulfide was distilled off in vacuum, the reaction mass was decomposed with ice water and extracted with ether; the ethereal solution was dried and distilled, and the residue distilled in vacuum (6 mm) at 184-187°. There was obtained 52 g (66%). The substance was dissolved in ether; slow removal of the solvent resulted in separation of large white crystals with m.p. 60-61°.

Methoxybenzophenone thiosemicarbazone was prepared similarly to benzophenone thiosemicarbazone. The obtained precipitate was washed with hot water and crystallized from 50% alcohol. Yield 60% of the theoretical. M.p. 183-184°.

* Communication I see: Proceedings of the Mendeleev All-Union Chemical Society, 1963, No. 2.

Found %: N 14.67; S 11.24. $C_{15}H_{15}ON_3S$ Calculated %: N 14.73, S 11.22.

3. p-Hydroxybenzophenone [3] was prepared by demethylation of p-methoxybenzophenone by heating to boiling a solution of p-methoxybenzophenone in 5 times the amount of glacial acetic acid containing 48% HBr for 10 hours. The solution was poured into water, neutralized with sodium carbonate and extracted with ether; the ether was distilled off and the residue dissolved in 5% sodium hydroxide. The insoluble residue was filtered off and the solution was acidified with hydrochloric acid to bring down the p-hyrdroxybenzophenone. Yield 72% of the theoretical. M.p. 133-134°.

p-Hydroxybenzophenone thiosemicarbazone was prepared by boiling an alcoholic solution of p-hydroxybenzophenone and thiosemicarbazide for 4 hours. At the end of the reaction, after cooling the solution, a precipitate did not come down. The alcohol was distilled off, the residue washed with hot water (in which it partly dissolved) and crystallized from 50% alcohol. White crystals with m.p. 188-190° were obtained. The product is soluble in ether, acetone and hot alcohol, insoluble in benzene and water. Yield 65% of the theoretical.

Found %: S 11.65; N 15.43. $C_{14}H_{13}ON_3S$. Calculated %: S 11.80; N 15.50.

4. p-Nitrobenzophenone was prepared by condensing p-nitrobenzoyl chloride with benzene (3 times the quantity) in presence of aluminum chloride at room temperature. The reaction mass was left overnight and on the following day it was heated at 45-50° for 2 hours. It was thereupon decomposed with ice water and the benzene was distilled off with steam. The residue was filtered, washed with 2% sodium hydroxide solution and recrystallized from alcohol.

M.p. 135°. Yield 90% of the theoretical.

When p-nitrobenzophenone was boiled with thiosemicarbazide in alcohol for 6 to 10 hours, it was recovered unchanged. With the addition of one to two drops of hydrochloric acid, the reaction was performed for 3 hours. When the alcoholic solution was cooled, a precipitate came down and was washed with hot water and recrystallized from 80% alcohol. M.p. 205-206°. Yield 75% of the theoretical. The substance is readily soluble in chloroform, insoluble in water. It crystallizes from alcohol and aqueous alcohol.

Found %: N 18.88; S 10.60. $C_{14}H_{12}O_2N_4S$. Calculated %: N 18.66; S 10.66.

5. p-Aminobenzophenone is prepared by reducing p-nitrobenzophenone with molecular hydrogen in presence of Raney nickel while shaking in a medium of alcohol at normal pressure and room temperature. The theoretical amount of hydrogen was absorbed. The reaction mass was heated and filtered, the alcohol was distilled off in vacuum and the residue extracted with a hot solution of dilute hydrochloric acid (1:5). The solution was treated with carbon and filtered; the amine was fractionally separated by addition of ammonia to the cold filtrate. Crystallization from aqueous alcohol gave white crystals with m.p. 123-124°. Yield 58% of the theoretical.

p-Aminobenzophenone thiosemicarbazone was prepared by heating an alcoholic solution of p-aminobenzophenone with thiosemicarbazide in presence of a drop of concentrated hydrochloric acid for 3 hours. On cooling, an insignificant amount of thiosemicarbazide was precipitated and was filtered off. The alcoholic filtrate was distilled in vacuum and the residue was repeatedly washed with ether and recrystallized from 50% alcohol. M.p. 155-157°. Yield 30%. Soluble in alcohol and acetone, slightly soluble in water.

Found %: N 20.51; S 11.91. $C_{14}H_{14}N_4S$. Calculated %: N 20.74, S 11.85.

6. p-Acetaminobenzophenone was prepared by heating p-aminobenzophenone with acetic anhydride on a boiling water bath for 2 hours. The solution was poured into water and the precipitate was recrystallized from aqueous alcohol. M.p. 150-151°. Yield 95% of the theoretical.

p-Acetaminobenzophenone thiosemicarbazone was prepared by heating an alcoholic solution of p-acetaminobenzophenone with thiosemicarbazide for 4 hours. After cooling, a precipitate came down from the solution and was washed with hot water before recrystallization from aqueous alcohol. M.p. (with decomp.) 240-241° (rapid melting). Yield 73% of the theoretical.

Found %: N 17.77; S 10.23. $C_{16}H_{16}ON_4S$. Calculated %: N 17.94, S 10.25.

7. p-Diacetylaminobenzophenone. p-Aminobenzophenone was heated with acetic anhydride on a gauze at the boil for 3 hours. The mass was then poured into ice water and the precipitate was recrystallized from

aqueous alcohol. M.p. 172-173°. Yield nearly theoretical. Analysis showed that the substance was the diacetyl derivative of p-aminobenzophenone, not described in the literature.

Found %: N 5.04; CH_3CO 30.3; H 5.63; C 73.02. $C_{17}H_{15}O_3N$. Calculated %: N 4.98; CH_3CO 30.6; H 5.34; C 72.62.

The same compound is obtained if p-acetaminobenzophenone (m.p. 150-151°) is heated with acetic anhydride on a gauze for 2 hours. Saponification with hydrochloric acid in alcohol gave p-aminobenzophenone.

p-Diacetaminobenzophenone thiosemicarbazone could not be prepared in the pure form. When this reaction was performed in the usual conditions, crystallization from alcohol gave a substance with decomposition point 228-230°. Judging by the analyses for S and acetyl group, this was a mixture of the thiosemicarbazones of mono- and diacetaminobenzophenone. It was impossible to separate and purify the components. Apparently partial cleavage of the acetyl group occurs during the reaction.

8. p,p'-Dinitrobenzophenone was prepared by oxidizing 1,1-dichloro-p,p'-dinitrodiphenylethylene with chromic acid in glacial acetic acid. M.p. 188-189°.

When an alcoholic solution of p,p'-dinitrobenzophenone had been heated with thiosemicarbazide for 6-10 hours, the starting products were recovered unchanged. With the addition of one drop of hydrochloric acid, or by the use of thiosemicarbazide hydrochloride, dinitrobenzophenone thiosemicarbazone was obtained in quantitative yield after only 2 hours. The compound is insoluble in alcohol, soluble in hot acetone, and is precipitated from the latter on addition of water. Decomposition point 243.5-244°.

Found %: S 9.05. $C_{14}H_{11}O_4N_5S$. Calculated %: S 9.27.

9. p,p'-Diaminobenzophenone [4] was prepared by condensation of acetanilide with carbon tetrachloride in presence of freshly distilled aluminum chloride, followed by saponification of the resultant p,p'-diacetaminobenzophenone. Saponification of the acetyl groups with dilute sulfuric acid invariably gave a considerable amount of acid-insoluble precipitate. Saponification was preferably effected with a mixture of one part acetic acid and two parts hydrochloric acid (18%) by heating on the boiling water bath under a reflux condenser for 2 hours. After dilution of the reaction mass with ten times the amount of water followed by neutralization with ammonia until non-acid to Congo, a precipitate came down. It was crystallized from alcohol. M.p. 241-242° (with decomp.).

Heating of diaminobenzophenone with thiosemicarbazide in alcohol failed to yield the expected thiosemicarbazone. Successful preparation was prepared in the following conditions: To a suspension of 2 g p,p'-diaminobenzophenone in 60 ml alcohol was added a solution of 1.6 g thiosemicarbazide hydrochloride in 6 ml water. The mixture was left overnight at room temperature. The precipitate of diamine formed a red solution. The alcohol was distilled off in vacuum and the residue was dissolved in water. The solution was filtered and neutralized with 3% sodium bicarbonate solution to give a precipitate weighing 2.1 g and decomposing at 193-194°. Repeated crystallization from aqueous alcohol raised the decomp. pt. to 207-207.5°. The hydrochloride is soluble in water.

Found %: S 11.16. $C_{14}H_{15}N_5S$. Calculated %: S 11.23.

10. p,p'-Diacetaminobenzophenone was prepared pure by acetylation of diaminobenzophenone with acetic anhydride. M.p. 237°. Yield 85% of the theoretical.

Unsuccessful attempts were made to prepare p,p'-diacetaminobenzophenone thiosemicarbazone by heating with thiosemicarbazide in alcoholic solution or in alcohol containing hydrochloric or acetic acid, by heating in butyl alcohol or in alcohol containing thiosemicarbazide hydrochloride.

SUMMARY

1. 8 Thiosemicarbazones of benzophenone and its derivatives were prepared.

2. This reaction was shown to be catalyzed by hydrochloric acid in a number of cases.

3. Tests of the prepared compounds against tuberculosis organisms in vitro showed that the thiosemicarbazones of this series are either inactive towards the bacilli or possess an extremely weak activity.

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Received July 11, 1952

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SYNTHESIS OF LEUCO BASES AND DYES OF THE TRIPHENYLMETHANE SERIES. II. [1]

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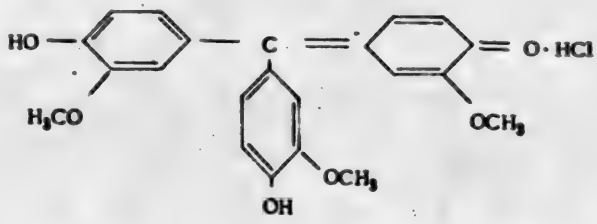
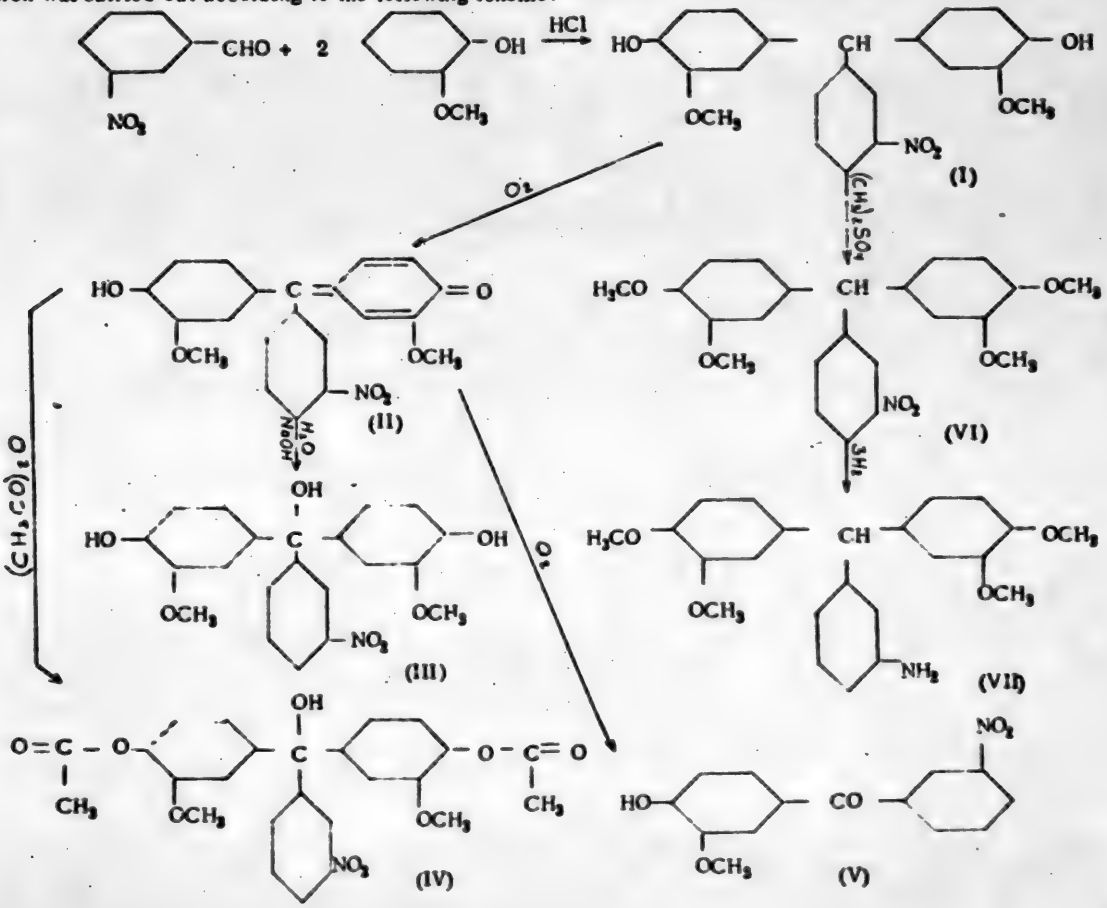
The preparation of rubrophen was disclosed in 1937 [2]. It is a dihydroxytrimethoxyfuchsone. Its hydrochloride is known to us by the name of rubrocol.



It proved to possess a very low toxicity and found application in the therapy of some nonpulmonaryforms of tuberculosis (tuberculosis of the glands [3,4], urinogenital tuberculosis [5], bone and joint tuberculosis). This prompted Soviet scientists to investigate compounds of the hydroxytriphenylmethane series [6,7], with the aim of finding more effective and more accessible agents for the cure of tuberculosis.

We have prepared compounds of the triphenylmethane series containing, in addition to hydroxy and methoxy groups, nitro, amino, sulfanilamino and other groups.

In this communication we describe 3-nitro-4',4"-dihydroxy-3',3"-dimethoxytriphenylmethane (I) and its transformation products. Starting materials for this synthesis were m-nitrobenzaldehyde and guaiacol. The research was carried out according to the following scheme:



Condensation of o-, m- and p-nitrobenzaldehydes with phenols and their ethers always gave amorphous, difficultly purifiable products which were characterized as pure substances on the basis of their analyses [8-11]. When the condensation of m-nitrobenzaldehyde with guaiacol was performed in a mixture of concentrated hydrochloric and glacial acetic acids, we obtained a crystalline substance in 90% yield which defied description; in analysis it corresponded to the product that we had expected to obtain—3-nitro-4',4"-dihydroxy-3',3"-dimethoxytriphenylmethane (I). Examination showed, however, that it was heterogeneous; after its saturated acetic acid solution had stood for a lengthy period (about 2 months), separation occurred of up to 10% of a crystalline nitro compound with m.p. 138-140° whose analysis also corresponded to compound (I). Oxidation of the amorphous product gave up to 40% of 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone (II), likewise identical with the product of oxidation of the crystalline nitro compound (I). Furthermore, from the residual reaction mass was isolated a dye differing in properties from the compounds of the hydroxyfuchsone series (is not decolorized by caustic alkalies); we did not examine it more closely.

Condensation of m-nitrobenzaldehyde with guaiacol in presence of dry hydrogen chloride gas gave the crystalline compound (I) in a yield of 70% of theory. It was oxidized with amyl nitrite in ethyl acetate which contained dry hydrogen chloride. The resultant 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone crystallizes with molecular ether, is readily hydrolyzed by water to form compound (II), and dissolves in caustic alkali with a bright-blue color. The color disappears when the alkaline solution stands in the air. From the decolorized alkaline solution of 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone was isolated 3-nitro-4',4"-dihydroxy-3',3"-dimethoxytriphenylcarbinol (III). Acetylation of 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone (II) with acetic anhydride gave 3-nitro-4',4"-diacetoxy-3',3"-dimethoxytriphenylcarbinol (IV). Passage of a current of air through the alkaline solution of the nitrofuchsone (II) gave its cleavage product (not described in the literature), 3-nitro-4'-hydroxy-3'-methoxybenzophenone (V). The nitrofuchsone (II) possesses valuable properties as an indicator.

With the aim of establishing the necessity of the presence of free hydroxy groups for the tuberculostatic action of hydroxytriphenylmethane compounds, we methylated these groups in 3-nitro-4',4"-dihydroxy-3',3"-dimethoxytriphenylmethane. Methylation was performed with dimethyl sulfate in an alkaline medium. The obtained 3-nitro-4',4",3',3"-tetramethoxytriphenylmethane (VI) was reduced with hydrogen in presence of skeletal nickel catalyst to form 3-amino-4',4",3',3"-tetramethoxytriphenylmethane (VII).

Examination of the tuberculostatic activity of the prepared compounds, carried out by O. O. Makeeva in the chemotherapeutic laboratory of the VNIKhFI under the direction of Professor G. N. Pershin, showed that leuco bases and dyes with free hydroxy groups possess slight activity against tuberculosis bacilli. Substitution of the hydroxy groups leads to complete loss of antitubercular activity.

EXPERIMENTAL

3-Nitro-4',4"-dihydroxy-3',3"-dimethoxytriphenylmethane (I)

Into a thoroughly triturated mixture of 46 g pure m-nitrobenzaldehyde and 82 g freshly distilled guaiacol was passed a steam of dry hydrogen chloride for 4 hours. The reaction mass was left overnight and then crystallized from 90 ml 80% acetic acid. 85 g substance with m.p. 133-136° was obtained. Crystallization from alcohol gave 78 g of a substance with m.p. 138-140°. It dissolves readily in glacial acetic acid (when heated), chloroform and caustic alkali; it has poor solubility in alcohol, ethyl acetate, acetone and ether; it is insoluble in benzene, petroleum ether, water, bicarbonate, sodium carbonate and ammonia. The caustic alkaline solution is colored yellow.

Found %: C 66.51, 66.55; H 4.97, 5.21; N 3.77, 3.83; OCH_3 16.12, 16.29. $C_{21}H_{19}O_6N$. Calculated %: C 66.14; H 4.98; N 3.67; OCH_3 16.29.

3-Nitro-4'-hydroxy-3',3"-dimethoxyfuchsone (II)

Into a four-necked flask, fitted with a stirrer and seal, a thermometer, a dropping funnel and a condenser topped by a calcium chloride tube, was introduced 25 g 3-nitro-4',4"-dihydroxy-3',3"-dimethoxytriphenylmethane and 150 ml dry ethyl acetate. The solution was cooled to a temperature of 0-2°, and addition was then made to it of 100 ml ethyl acetate containing 25 g dry hydrogen chloride. The solution turned red-violet. A solution of 20 ml freshly distilled amyl nitrite in 20 ml dry ethyl acetate was then stirred in gradually from the dropping funnel. With the addition of the first drop of solution the color changed to dark violet. The duration of the addition was 2 hours. Stirring at a temperature of 5-6° was continued for a further 3 hours and the reaction mass was left overnight at a temperature not higher than 15°. On the following morning the bottom of the flask contained an abundant, dark-violet precipitate of the hydrochloride. This was filtered off and washed with ethyl acetate and dry ether. For removal of the ethyl acetate it was left in dry ether for another few hours. The hydrochloride melted at 182-184° (with decomp.). Its chlorine analysis corresponds to 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone hydrochloride.

containing one molecule of ether of crystallization.

Found %: Cl 7.29, 7.25. $C_{21}H_{17}O_6N \cdot HCl \cdot C_4H_{10}O$. Calculated %: Cl 7.26.

The hydrochloride is completely hydrolyzed by water in 2-3 hours. Its solution in 10% hydrochloric acid is almost completely hydrolyzed. When the hydrochloride is treated with sodium acetate solution it is also converted into the base after a few hours; after standing for a long period, the solution turns blue.

The base obtained by treating the hydrochloride with water is an orange, crystalline powder, with m.p. 227-228°. From glacial acetic acid it forms bright-orange crystals reminiscent of potassium bichromate in color; m.p. 228-229°. Its analysis corresponds to 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone.

Found %: C 66.36, 66.52; H 4.65, 4.67; N 3.71, 3.67. $C_{21}H_{17}O_8N$. Calculated %: C 66.49; H 4.48; N 3.69.

When the nitrofuchsone (II) is heated with 20% sodium bisulfite solution for 1-1½ hours at 60-70°, it partly goes into solution. The bisulfite compound does not crystallize from the solution. Addition of concentrated hydrochloric acid to the bisulfite solution brings down crystals of the hydrochloride of the nitrofuchsone contaminated by crystals of sodium chloride. Heating with hydrochloric acid gave a substance which did not yield the pure nitrofuchsone (II) after treatment with water. the substance has a low and prolonged melting range. The bisulfite solution becomes blue when treated with caustic alkali.

Hydrate form of 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone. 0.5 g 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone was dissolved in 20 ml glacial acetic acid and the solution was poured dropwise into 100 ml water. The resultant flocculent, orange precipitate was dried in a vacuum-desiccator over caustic alkali for 2 days. It melted with gradual shrinkage at 80-90°, after which it again solidified and finally melted at 227-228°. Its analysis for water of crystallization showed that it contains slightly less than 1 mole. It probably loses some water of crystallization in the desiccator.

Found %: H_2O 4.00, 4.08. $C_{21}H_{17}O_6N \cdot H_2O$. Calculated %: H_2O 4.53.

Recrystallization of the nitrofuchsone from glacial acetic acid gave a product melting at 228-229°. The hydrated form forms a bisulfite compound rather more quickly than the crystalline product, but a considerable proportion of the former likewise does not go into solution.

3-Nitro-4',4"-dihydroxy-3',3"-dimethoxytriphenylcarbinol (III)

1 g nitrohydroxydimethoxyfuchsone (II) was dissolved in 100 ml 5% sodium hydroxide to give a bright-blue solution. This was filtered. After 15-25 minutes it had lost the blue color and become red-orange and then brown. The color of the solution did not undergo any further change. The alkaline solution of the fuchsone was cooled while dropwise addition was made to it of 100 ml of 40% sodium bisulfite solution. A white flocculent precipitate was formed. This was filtered, washed with distilled water and dried on filter paper. A part of it was dried out in a vacuum-desiccator over sodium hyroxide. A slightly greyish powder was obtained with inclusions of orange material. Another portion was crystallized from aqueous acetone; when the solvent was slowly evaporated, white crystals came down in the form of cubes melting at 158-160°. The recrystallized material was kept in a desiccator for about a week and remained white, but afterwards turned yellow. The color of the uncrystallized precipitate changed to orange after only a day. Addition to the acetone solution of the carbinol of one drop of ammonia caused it to turn green, while one drop of concentrated hydrochloric acid turned it red-violet. The color hardly changed when dilute hydrochloric acid (2% solution) was added to the solution.

Found %: N 3.45, 3.54. $C_{21}H_{19}O_7N$. Calculated %: N 3.52.

3-Nitro-4',4"-diacetoxy-3',3"-dimethoxytriphenylcarbinol (IV)

To 2 g 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone was added 15 ml acetic anhydride and 0.5 g anhydrous sodium acetate; the solution was heated on a gauze to boiling for 3 hours, the color becoming light-orange and remaining so. After completion of the reaction, the solution was diluted with acetic acid and poured into ice water dropwise. The resultant slightly cream-colored, flocculent precipitate was not crystallized but was quickly washed with 2% sodium hydroxide solution, dissolved in acetic acid and the solution poured into water. It melted gradually between 76 and 80°.

Found %: $COCH_3$ 17.04; OH 3.85; N 2.91, 3.05. $C_{25}H_{23}O_9N$. Calculated %: $COCH_3$ 17.80; OH 3.53; N 2.91.

Analysis for the hydroxyl group by Tserevitinov's method confirmed the formation of the carbinol during acetylation.

Oxidative-alkaline cleavage of 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone

3-Nitro-4'-hydroxy-3'-methoxybenzophenone (V)

Into a 2-necked flask, fitted with a condenser connected at the top to a water jet pump and with a rubber stopper through which passed a bent tube reaching to the bottom of the flask, was introduced 2 g 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone (II) and 100 ml 5% sodium hydroxide solution. The bent tube was connected to two wash-bottles two-thirds filled with 20% sodium hydroxide solution. Aspiration of air was regulated by opening the pump so that not more than 2-3 bubbles passed through per second. The reaction flask was placed in a boiling water bath. After 15 hours a light-yellow precipitate had formed. The reaction flask was stood for a further 24 hours and then the precipitate was filtered off (0.8 g). It was dissolved in 30 ml water, the solution was filtered, and carefully neutralized (while cooling) with 40% acetic acid. 0.65 g of slightly pinkish precipitate was separated. It was crystallized from 5 ml alcohol to give slightly pinkish crystals with m.p. 132-134°. A second crystallization from alcohol raised the m.p. to 134-135°. Yield 0.4 g. A further recrystallization did not change the melting point.

The substance is soluble in the cold in caustic alkali to a bright-yellow solution; when heated it dissolves in 15% sodium carbonate solution with a green color; it does not dissolve on heating in 5% sodium carbonate solution, in bicarbonate and water, but the solvent takes on a greenish color. It dissolves in alcohol, acetone, ether and chloroform.

Its analysis corresponds to 3-nitro-4'-hydroxy-3'-methoxybenzophenone, not described in the literature. Its structure follows from the structure of the initial fuchsone and can only be 3-nitro-4'-hydroxy-3'-methoxybenzophenone.

Found %: C 61.77, 61.61; H 4.03, 4.17; N 5.18, 5.23. $C_{14}H_{11}O_5N$. Calculated %: C 61.54; H 4.03; N 5.12.

Indicator properties of 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone

We prepared buffer solutions from borax and monosubstituted potassium phosphate with pH from 6 to 7.6. The solutions were prepared in gradations of 0.1 pH. In addition, an 0.5% solution of 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone in acetone was prepared.

In a test tube were placed 10 ml buffer solution and 3-4 drops of the acetone solution of the dye. We observed sharp color changes at any pH interval:

at pH 6.4 the color was yellow, at pH 6.6, it was green, at pH 7.1 it was dark blue. The results were checked by titration.

3-Nitro-3',3",4',4"-tetramethoxytriphenylmethane (VI)

Into a thick-walled, round-bottomed flask were introduced 9 g 3-nitro-4',4"-dihydroxy-3',3"-dimethoxytriphenylmethane, 24 ml 10% sodium hydroxide and 7.2 ml dimethyl sulfate. The flask was vigorously shaken for 20-25 minutes. An oily substance separated out and later solidified to a clot. This was separated from the solution, pulverized, washed 2-3 times with 2% sodium hydroxide solution (5-10 ml each time) and then with water until the alkaline reaction had disappeared. The precipitate was dried and crystallized first from acetone and then from alcohol. There was obtained 7 g of yellow, finely crystalline product with m.p. 138-139° (73% of theory). The product gives a sharp depression of m.p. in the mixed melting test with the original nitro compound. It is insoluble in caustic alkali, very slightly soluble in alcohol and acetone.

Found %: N 3.68, 3.65; OCH_3 29.85, 29.80. $C_{23}H_{23}O_6N$. Calculated %: N 3.42; OCH_3 30.32.

3-Amino-3',3",4',4"-tetramethoxytriphenylmethane (VII)

5 g of (VI) was dissolved in 100 ml alcohol and to the solution was added 5 g skeletal nickel catalyst. The flask was connected to an apparatus filled with hydrogen and shaken on the machine. At the end of the reduction a considerable precipitate had formed. The reaction mixture was heated to the boil and the catalyst filtered off. Cooling of the filtrate led to separation of 2.3 g of substance. After driving off the solvent a further 1.7 g was obtained in the form of white needles with m.p 126-127°. Yield 95% of theory. Repeated crystallization did not alter the melting point of the compound.

Found %: N 3.66, 3.77; OCH_3 32.42, 32.30. $C_{23}H_{25}O_6N$. Calculated %: N 3.69; OCH_3 32.74.

3-Amino-2',3",4', 4"-tetramethoxytriphenylmethane hydrochloride.

Treatment of the amine with 10% hydrochloric acid solution gave the water-insoluble hydrochloride. It crystallizes from alcohol with m.p. 230-232°; it is insoluble in concentrated and dilute hydrochloric acid, soluble in water when heated. The chlorine was determined by potentiometric titration.

Found %: Cl 8.50, 8.48. $C_{23}H_{25}O_4N \cdot HCl$. Calculated %: Cl 8.53.

SUMMARY

1. A series of hydroxytriphenylmethane compounds was synthesized.

2. The transformations of 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone were studied; its carbinol base and the product of its acetylation and oxidative cleavage were prepared.

3. The indicator properties of 3-nitro-4'-hydroxy-3',3"-dimethoxyfuchsone were studied. It shows a sharp color change in the pH region of 6.4 to 7.1 and may be recommended as an indicator for titration.

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Received July 11, 1952

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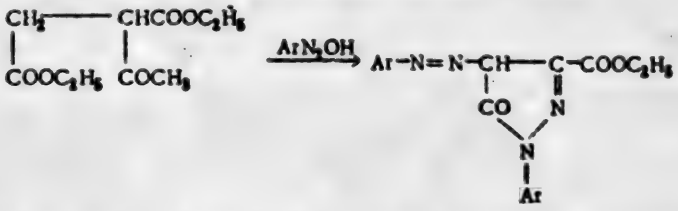
ACTION OF AROMATIC DIAZO COMPOUNDS ON COMPOUNDS OF THE TYPE OF ALKYLACETOACETIC ESTERS AS A METHOD OF SYNTHESIZING ARYL HYDRAZONES OF α-KETO ACIDS, α-AMINO ACIDS AND HETEROCYCLIC NITROGEN COMPOUNDS

XIII. REACTION OF DIETHYL α-ACETOGLUTARATE AND SOME OF ITS ANALOGS WITH ARYLDIAZONIUMS

V. V. Feofilaktov and N. K. Semenova

In a series of previous communications one of us demonstrated the possibility of applying the coupling reaction of aryldiazoniums with compounds of the type of alkylacetoacetic esters to the preparation of arylhydrazones of α-keto acids, as well as the application of the latter to the synthesis of α-amino acids [1-13] and indole derivatives [14].

It was also established that the arylhydrazones of esters of oxaloacetic acid, formed by coupling aryldiazoniums with acetosuccinic ester, spontaneously (even in process of their formation) were capable of ring closure to form a pyrazolone ring, and that the latter there and then again undergoes azo coupling with formation of azo compounds of the pyrazolone series [15,16]:

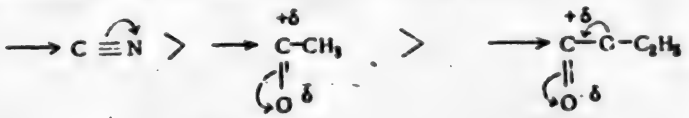


It appeared to be of interest to study the azo coupling of arylhydrazones with α-acetoglutaric ester and some of its analogs: γ,γ-diacetobutyric, α-carbethoxyglutaric and β-cyanoethylacetoacetic esters, and to make use of the resultant arylhydrazones for further syntheses. In particular we had in mind the investigation of the possibility of utilizing them for the synthesis of six-membered nitrogen heterocycles – pyridazinones – which have so far received little attention.

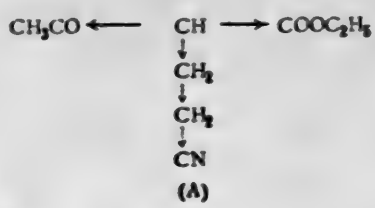
Coupling was performed in aqueous-alcoholic acetic acid, neutral or alkaline media, depending on the character and activity of the diazo and azo components. It was established that diazo components containing electrophilic substituents in the ring (p-nitroaniline, sulfanilic and anthranilic acids, etc.), also α- and β-naphthylamines, coupled in acetic acid and neutral media, diazo components containing nucleophilic substituents (toluidines) coupled in an alkaline medium, in agreement with statements in the literature [17].

In our case the more active azo components proved to be β-cyanoethylacetoacetic and γ,γ-diacetobutyric esters, and the less active ones were α-acetoglutaric and α-carbethoxyglutaric esters. We arrive at this conclusion both on the basis of the ability of the former to couple in acetic acid and neutral media and on the basis of the higher yields of their coupling products, as can be illustrated by the reaction with phenyldiazonium chloride (Table 1).

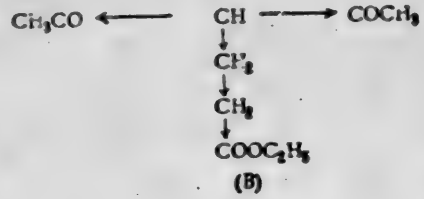
The differing activity of these esters as azo components, as revealed in our experiments, can be correlated with the character and number of the groups activating the prototropic systems; as we know [18], these groups can be arranged in the following order in respect of their activating energy:



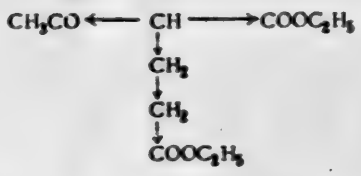
On comparing the structures of the esters



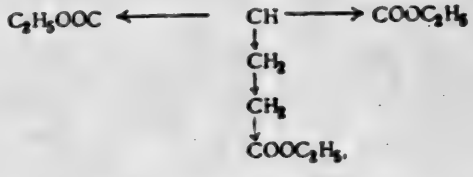
(A)



(B)



(C)



(D)

we notice at once that among the activating groups of (A) and B) there are two each of the more active electrophilic groups (CN; CH_3CO), while the third contains only one of these (CH_3CO), and the fourth (D) contains three of these but the least active ones ($COOC_2H_5$). Hence the hydrogen of the CH groups in the first two compounds is more positive (labile) than in the third and fourth; this property is a factor in their differing activity as azo components.

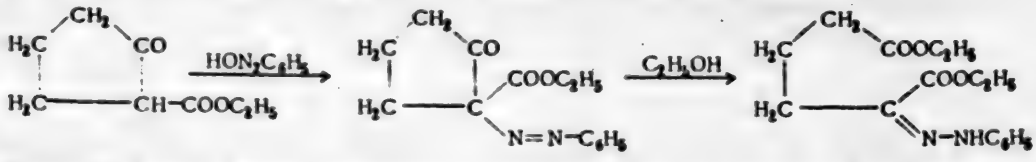
TABLE 1

Azo component	Coupling medium	Yield of hydrazone (%)
β-Cyanoethylacetoacetic ester	Neutral	98
γ,γ-Diacetobutyric ester	Neutral	90.1
α-Acetoglutaric ester	Acetic acid	71
α-Carbethoxyglutaric ester	Caustic alkali	49

The result of azo coupling, as a rule, is the formation of amorphous, brown, oily products (azo esters). In the case, however, of α-acetoglutaric ester and naphthionic acid as the diazo components, it was possible to isolate the azo esters in the solid form and to analyze them as the sodium salts (Table 2, Formula 12).

As a general rule, the process of coupling of all these esters was accompanied by separation of appreciable amounts (perceptible by the odor) of ethyl acetate. It is formed apparently by addition to some extent of alcohol (or alcoholate) to the acetyl group of the azo ester and subsequent cleavage of this group in the form of ethyl acetate. A similar type of alcoholysis at the $>C=O$ group was previously observed by one of us [14a] and by Hauser and Reynolds [19].

By carrying out the coupling of cyclopentanone carboxylic ester with diazobenzene in an alcoholic medium there is obtained, in addition to the phenylhydrazone of the acid ester of α-ketoadipic acid, a small amount of the phenylhydrazone of the diethyl ester of α-ketoadipic acid. Formation of the latter may be regarded as an unusual case of alcoholysis, although proceeding in presence of considerable amounts of water [14a]:



Hauser and Reynolds observed the addition of alcohol (in the form of alcoholate) to the benzoyl group of the ethyl ester of α-nitroso-α-benzoylvaleric acid and subsequent cleavage in the form of ethyl benzoate.

In the course of our research we also observed that the ease of cleavage of the CH_3CO- and C_2H_5COO- groups from the azo esters depends in large measure on the character and structure of the azo and diazo components. It is higher in the case of the products of the coupling of more active components and lower in the case of azo esters prepared by coupling of less active components. Thus, of the five products of coupling of phenyldiazonium chloride with various esters, only one (with β-cyanoethylacetoacetic ester) underwent

TABLE 2

Products of Coupling of α-Acetoglutaric Ester with Aryldiazoniums

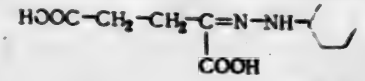
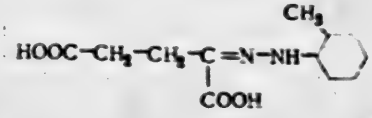
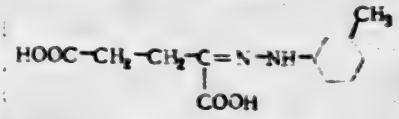
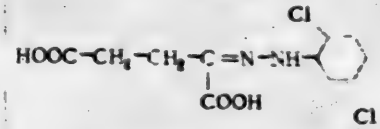
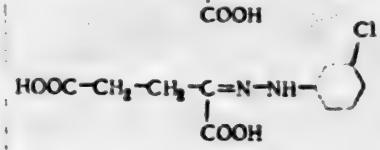
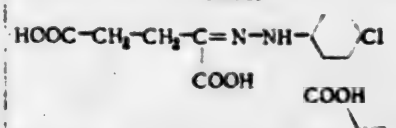
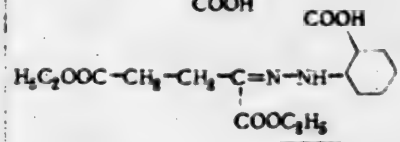
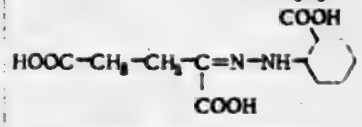
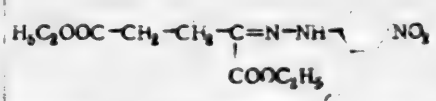
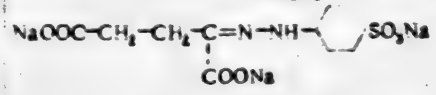
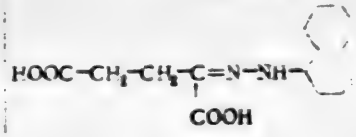
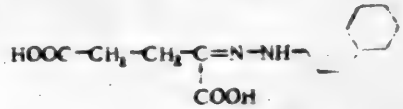
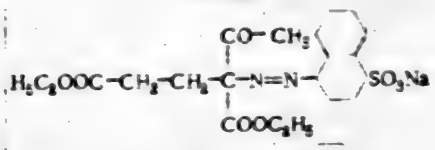
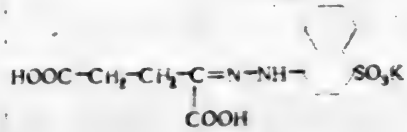
Prep. No.	Diazo component	Structure of product	M.p. (uncorrected)	Yield (%)
1	Aniline		152-153° [28]	74
2	o-Toluidine		159-160	88
3	m-Toluidine.		149	33.6
4	o-Chloroaniline. . .		183 [31]	60
5	m-Chloroaniline . .		170-171 [31]	72.1
6	p-Chloroaniline. . .		166	81
7	Anthranilic acid . .		104-105	57
7a	Ditto		225	–
8	p-Nitroaniline. . . .		137	87
9	Sulfanilic acid . . .		does not melt	95.3
10	α-Naphthylamine .		171	47.2
11	β-Naphthylamine. .		150	33.1
12	Naphthionic acid. .		does not melt	78.5
12a	Ditto.		does not melt	–

TABLE 3

Products of Coupling with Aryldiazoniums of Some Analogs of α-Acetoglutaric Ester

Prep. No.	Azo component	Diazo component	Structure	M.p.	Yield (%)
1	$NC-CH_2-CH_2-CH(COOC_2H_5)(CO-CH_3)$	Aniline	$NC-CH_2-CH_2-C(COOC_2H_5)=N-NH-C_6H_5$	159°* [29]	98
2		p-Nitroaniline	$NC-CH_2-CH_2-C(COOC_2H_5)=N-NH-C_6H_4-NO_2$	158	98
3	$C_2H_5OOC-CH_2-CH_2-CH(CO-CH_3)(CO-CH_3)$	Aniline	$HOOC-CH_2-CH_2-C(CO-CH_3)=N-NH-C_6H_5$	173-174	90.1
4		o-Toluidine	$HOOC-CH_2-CH_2-C(CO-CH_3)=N-NH-C_6H_4-CH_3$	150	72.4
5		m-Toluidine	$HOOC-CH_2-CH_2-C(CO-CH_3)=N-NH-C_6H_4-CH_3$	155	85.5
6		p-Toluidine	$HOOC-CH_2-CH_2-C(CO-CH_3)=N-NH-C_6H_4-CH_3$	167	80.6
7		p-Nitroaniline	$C_2H_5OOC-CH_2-CH_2-C(CO-CH_3)=N-NH-C_6H_4-NO_2$	132	84.6
8	$C_2H_5OOC-CH_2-CH_2-CH(COOC_2H_5)(COOC_2H_5)$	Aniline	$HOOC-CH_2-CH_2-C(COOH)=N-NH-C_6H_5$	152-153	49.1

spontaneous cleavage of the CH_3CO- group without supplementary reaction (Table 3: 1), whereas in the case of the products of coupling of γ,γ-diacetobutyric, α-acetoglutaric and α-carbethoxyglutaric esters, treatment was necessary with caustic alkali solution; for the first component the treatment could be less drastic (at room temperature or with gentle heating), but the others require reaction at the boil (on a water bath or gauze).

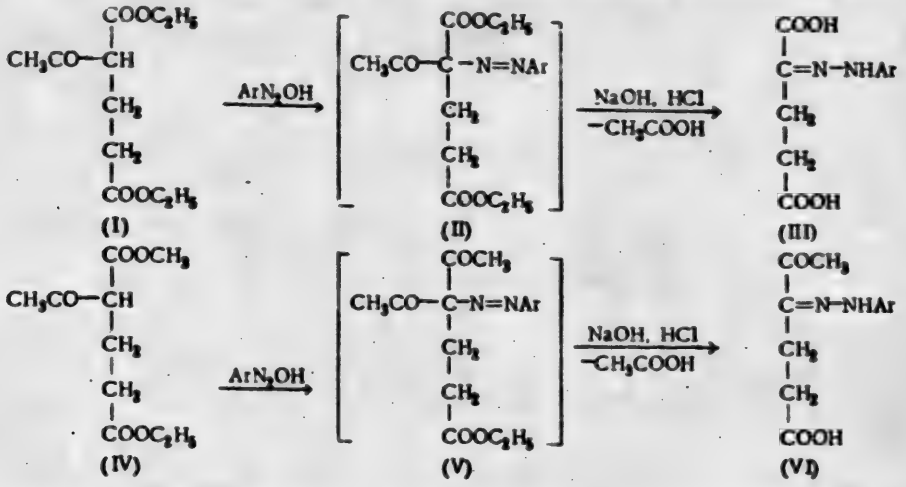
On the other hand, when the azo component was p-nitroaniline, then in the case of β-cyanoethylacetoacetic ester (Table 3, 2) and γ,γ-diacetobutyric ester (Table 3; 7) the cleavage of the acetyl group from the products of coupling proceeded spontaneously, and 10 minutes heating with 10-15% alcoholic solution of hydrochloric acid was only required for the azo esters prepared from α-acetoglutaric ester (Table 2; 8).

These observations of ours are in full accord with the conclusions from the investigations of M. M. Shemyakin and his coworkers [20-24] on the activating action on the hydrolytic cleavage of −C−C− bonds of electrophilic substituents and in particular of the NO_2 group, which in our experiments is readily transmitted through the conjugated double bond system of the benzene ring.

For the purpose of studying in more detail the behavior of α-acetoglutaric ester (I) during azo coupling and especially during subsequent saponification of the formed azo esters (II, V) a parallel study was made of the azo coupling of the ethyl ester of γ,γ-diacetobutyric acid (IV) with the same diazoniums. Saponification of the brown, amorphous products of azo coupling −the azo esters (V) • −gives well-crystallizable γ-arylhydrazones of β-pyruvylpropionic acid (VI: Table 3; 3,7), which are found to be quite different from the corresponding products of azo coupling of α-acetoglutaric ester (Table 2).

• This azo coupling reaction is likewise accompanied by formation of ethyl acetate (detected by odor).

Consequently, out of the two conceivable directions of hydrolytic cleavage of the azo esters (II) obtained from α-acetoglutaric ester, hydrolysis exclusively proceeds in the direction of cleavage of the acetyl groups (II ⟶ III), and does not proceed at all in the direction of cleavage of the carboethoxy groups (II ⟶ VI).



A comparative study of the behavior as azo components of α-carbethoxyglutaric ester and β-cyanoethylacetoacetic ester permitted the establishment of the advantages of some of these starting compounds for preparative purposes.

The prepared arylhydrazones were subjected to the following investigations:

a) Their transformation into indole derivatives, giving a comparatively convenient method for the synthesis of heteroauxin and its substituted products.

b) Reduction of some of them to glutamic acid, which on the whole, by extending to monoaminodicarboxylic acids the method of preparation of α-amino acids via the stage of the arylhydrazones of α-keto acids, gives a convenient method of synthesis of glutamic acid.

c) The ability of these arylhydrazones to cyclize to pyridazinone derivatives; investigations of some of the transformations of the latter.

EXPERIMENTAL

I. α-Acetoglutaric ester – Products of Its Azocoupling (Table 2).

α-Acetoglutaric ester was prepared by reaction of sodium ethyl acetoacetate with the ethyl ester of β-chloropropionic acid by the method of Clemo and Welch [25] as simplified by McIlwain and Richardson [26]. The ethyl ester of β-chloropropionic acid was synthesized by us from acrylonitrile by a slight modification of the known method [27].

Ethyl ester of β-chloropropionic acid Into a round-bottomed 500 ml flask placed in a freezing mixture (ice and salt) is poured 53 g (1 mole) freshly distilled acrylonitrile. The flask is corked; through the cork passes a reflux condenser and through the latter is passed a glass tube reaching to the bottom of the flask. A dry stream of hydrogen chloride is run into the acrylonitrile through the tube until the weight increases by 43 g (instead of 36 g); this takes 12-13 hours. Into the flask is then introduced 55 ml concentrated hydrochloric acid (specific gravity 1.19), the mixture is shaken and allowed to stand. After 5-10 minutes, vigorous saponification commences with considerable heat development and separation of an abundant precipitate of ammonium chloride. After 30-40 minutes, the flask is heated for 20-25 minutes on the water bath, and then addition is made of 60 ml absolute ethyl alchol before continuing the heating for another 30 minutes. The cooled mixture is agitated with 125 ml cold water, the β-chloropropionic ester is separated, washed with 5% sodium carbonate solution and with water, dried with anhydrous sodium sulfate and distilled on an oil bath. a fraction is collected at 162-163°. Weight 105 g (78% calculated on the acrylonitrile).

Diethyl ester of α-acetoglutaric acid Into a round-bottomed flask (500 ml), fitted with a reflux condenser and calcium chloride tube, is introduced 165 ml absolute ethyl alcohol and 11.5 g metallic sodium. To the cooled

alcoholate is added 130 g ethyl acetoacetate, followed after stirring by 68 g ethyl ester of β-chloro propionic acid. After a few minutes a vigorous reaction commences to the accompaniment of strong heat development and separation of sodium chloride. After an hour, the mixture is heated on the water bath (until the alkaline reaction disappears), the alcohol is distilled off, and to the cooled residue is added cold water (200 ml); the oily product is separated and washed with cold water; the wash liquors are extracted with ether which dissolves the main product, and the ethereal solution is dried with anhydrous sodium sulfate. After distilling off the solvent, the oily product is fractionated in vacuum to give a fraction boiling at 163-164° (22 mm); the weight of the α-acetoglutaric ester was 98.5 g or 85% (calculated on the β-chloropropionic ester) n_D^{19} 1.4420, d_4^{19} 1.0695; literature data: b.p. 146-147° at 12 mm [26].

Phenylhydrazone of α-ketoglutaric acid (Table 2: 1). 4.65 g of aniline was diazotized in the usual manner; the excess hydrochloric acid was removed by adding solid sodium acetate and the diazo solution was stirred in a thin stream into the sodium compound prepared from 11.5 g α-acetoglutaric ester, 1.15 g metallic sodium and 30 ml alcohol, contained in a beaker immersed in a freezing mixture (ice and salt). On mixing of the solutions, a yellow emulsion was formed and quickly separated a thick, dark-red oil. The odor of ethyl acetate was perceptible. Stirring was continued for 40-50 minutes until the diazo test gave a negative reaction (β-naphthol), after which the oil was separated, it did not crystallize on standing and was therefore saponified with 20% alcoholic sodium hydroxide • by heating on the water bath for 1-1½ hours.

After distilling off the alcohol, addition of water and extraction with ether of the neutral impurities, the cooled alkaline solution was acidified with dilute hydrochloric acid. The separated light-brown crystals of the phenylhydrazone of α-ketoglutaric acid were separated, washed with water and dried. Weight 8.75 g (74% of the theoretical), m.p. 145-148°. After recrystallization from alcohol (with addition of carbon) and then from ethyl acetate, the light-yellow crystals of the phenylhydrazone melted at 152-153°, •• in agreement with the literature [28].

Found %: N 11.71, 11.65. $C_{11}H_{12}O_4N_2$. Calculated %: N 11.86.

o-Tolylhydrazone of α-ketoglutaric acid (Table 2: 2). To a mixture of 5.3 g o-toluidine and 30 ml water in a beaker is added 13 ml concentrated hydrochloric acid followed by 40 g ice, the beaker is placed in a freezing mixture and at a temperature of −2 to −5° addition is gradually made of a solution of 3.6 g sodium nitrite in 14 ml water. After 10-15 minutes the diazotization is completed and the diazo solution is transferred with stirring into a beaker (immersed in freezing mixture and fitted with a mechanical stirrer) containing the sodium compound prepared from 11.5 g (0.05 mole) α-acetoglutaric ester, 4.6 g (0.2 g-atom) sodium metal and 60 ml absolute alcohol. A yellow emulsion forms and the smell of ethyl acetate is noticed. Stirring is continued for an hour (until the reaction for diazo compound is negative). The reaction product is a dark-red, oily azo ester; it is separated by decantation from the alcoholic liquor, the latter is acidified with HCl (to Congo) and twice extracted with ether; the ether is distilled off and the extract (about 0.4 g) is added to the azo ester. The combined product is dissolved in 40 ml 20% alcoholic solution of sodium hydroxide and refluxed on a water bath. After a heating period of 2½ hours, 40 ml water is added to the flask and the alcohol is distilled off. After removal of the neutral impurities by ether extraction, the cooled alkaline solution is acidified with dilute hydrochloric acid. The precipitated dark-yellow crystals are collected, washed with water and dried. Weight 11.0 g. Yield 88%. M.p. 155-157° (with decomposition); after recrystallization from hot acetic acid or 50% aqueous alcohol with addition of carbon, the yellow star-like clusters of needles of o tolyhydrazone of α-ketoglutaric acid melted at 159-160° with decomposition (uncorrected).

The compound is extremely soluble in acetone, readily soluble in ether, ethyl acetate, hot acetic acid and alcohol, poorly soluble in benzene. It forms a stable violet color with concentrated sulfuric acid and potassium bichromate (Bülow reaction).

Found %: N 11.01, 10.98, equiv. 122, 123. $C_{12}H_{14}O_4N_2$. Calculated %: N 11.20; equiv. 125.

m-Tolylhydrazone of α-ketoglutaric acid (Table 2: 3). 5.3 g m-toluidine was diazotized and coupled with the sodium derivative prepared from 11.5 g α-acetoglutaric ester by the previously described method. Saponification of the oily product of azo coupling was performed by heating with sodium alcoholate (4 g Na in 60 ml alcohol) for 2 hours. On the expiration of this period, addition was made to the flask of 100 ml water and the alcohol was distilled off. The neutral impurities were removed from the cooled alkaline solution by ether extraction and then the solution was carefully acidified (with ice cooling) with dilute hydrochloric acid. The resultant light-yellow

• 40% ethyl alcohol was normally used for the alcoholic alkali.

•• The melting points given for our preparations were not corrected.

crystals were collected, washed with water and dried. Weight 4.20 g (33.6 %), m.p. 146-148°. Readily soluble in methyl alcohol, ethyl alcohol, acetone and ethyl acetate. After recrystallization from aqueous ethyl alcohol, the m-tolylhydrazone of α-ketoglutaric acid melted at 149° with decomposition.

Found %: N 11.24, 11.30; equiv. 126, 127. $C_{12}H_{14}O_4N_2$. Calculated %: N 11.20; equiv. 125.

The obtained m-tolylhydrazone of α-ketoglutaric acid was converted into 1-(m-tolyl)-pyridazinone-3-carboxylic acid and 4-methyl-2-carboxyindole-3-acetic acid.

o-Chlorophenylhydrazone of α-ketoglutaric acid (Table 2; 4). 6.34 g o-chloroaniline was diazotized in the usual manner and the excess of hydrochloric acid removed with solid sodium acetate. With energetic stirring, the diazo solution was introduced portionwise into the cooled (with snow and salt) sodium derivative prepared from 11.5 g α-acetoglutaric ester, 1.15 g sodium and 30 ml absolute alcohol. The stirring was prolonged for an hour (until absence of free diazo). The separated dark-red oil was dissolved in 50 ml 25% alcoholic solution of potassium hydroxide and refluxed on the water bath. At the expiration of 4 hours, 30 ml water was added to the flask and the alcohol was distilled off. After removal of neutral impurities from the cooled alkaline solution by ether extraction, the solution was placed in a freezing mixture and acidified with dilute hydrochloric acid. The precipitated light-pink crystals were collected, washed with water and dried. Weight [illegible] g (60%), m.p. 176-179°, positive Bülow reaction. The crystals are highly soluble in ethyl acetate and acetone, dissolve readily in acetic acid and methyl and ethyl alcohols; they are insoluble in benzene, ligroin and ether; sparingly soluble in hot water. After recrystallization from alcohol (with carbon) and then from acetic acid, the bright-yellow needles melted at 183° with decomposition.

Found %: N 10.24, 10.22; equiv. 130,134. $C_{11}H_{11}O_4N_2Cl$. Calculated %: N 10.37; equiv. 135.

m-Chlorophenylhydrazone of α-ketoglutaric acid (Table 2; 5). 6.35 g m-chloroaniline was diazotized and coupled with the sodium derivative prepared from 11.5 g α-acetoglutaric ester in conditions similar to those employed with o-chloroaniline. After saponification of the dark-red oil, 9.75 g (72.1%) of dark-brown crystals was isolated, m.p. 166-168°. The crystals were readily soluble in ethyl and methyl alcohol, ether, acetone and ethyl acetate, much less soluble in benzene and ligroin, sparingly soluble in water. After three recrystallizations from 50% acetic acid in presence of carbon, the dark-red crystals of the m-chlorophenylhydrazone of α-ketoglutaric acid melted at 170-171° with decomposition and did not give Bülow's reaction.

Found %: N 10.32, 10.41; equiv. 132, 133. $C_{11}H_{11}O_4N_2Cl$. Calculated %: N 10.37; equiv. 135.

p-Chlorophenylhydrazone of α-ketoglutaric acid (Table 2; 6). 6.35 g p-chloroaniline was diazotized and coupled with the sodium derivative prepared from 11.5 g α-acetoglutaric ester in conditions similar to those employed for o-chloroaniline. The reaction product (a dark-red oil) was saponified with 50 ml 25% alcoholic potash by heating on the water bath for 5-6 hours. Acidification of the dilute alkaline solution gave 10.93 g (81%) yellow-pink crystals melting at 155-158° and not giving the Bülow reaction. The solubility was extremely good in acetone and ethyl acetate, good in ether, ethyl and methyl alcohols, hot acetic acid and boiling water; the product was insoluble in benzene. After two recrystallizations from boiling water in presence of carbon, the bright-yellow heavy crystals of the p-chlorophenylhydrazone of α-ketoglutaric acid melted at 166° with decomposition.

Found %: N 10.26, 10.55; equiv. 129, 133. $C_{11}H_{11}O_4N_2Cl$. Calculated %: N 10.37; equiv. 135.

o-Carboxyphenylhydrazone of diethyl α-ketoglutarate (Table 2; 7). 4.35 g anthranilic acid was mixed with 35 ml hot water to which was added 14 ml concentrated hydrochloric acid. The hydrochloride, cooled to −5°, was diazotized with 20% sodium nitrite solution (1.83 g in 8 ml water). Diazotization was continued for 20 minutes, after which the solution was kept in a freezing mixture for another 30 minutes (the excess of hydrochloric acid was not removed) and then transferred in a thin stream into a cooled solution of the sodium derivative of α-acetoglutaric ester with vigorous stirring. The sodium derivative was prepared from 5.8 g ester, 1.7 g sodium and 30 ml absolute alcohol. Mixing of the solutions caused a yellow emulsion to be formed, followed by separation of orange-colored oily drops and, finally, by a thick, dark-red oil, the odor of ethyl acetate was perceptible. After 40 minutes stirring, addition was made to the mixture of 10% NaOH solution until the reaction was neutral, and stirring was continued for another 40 minutes. The dark-red oil was extracted with ether and kept at room temperature, after two days it had solidified but no crystals were observed. The solid red mass, apparently a sodium salt (combined at the nuclear COOH group), was heated with a small amount (5 ml) dilute acetic acid. This again converted it into a red oil. The latter was separated from the acetic acid and triturated with cold ethyl alcohol (10-15 ml). It then solidified to a light-yellow, finely granular mass which was drained, washed with water and dried. Weight

4.78 g (57%), m.p. 101-104°, positive Bülow reaction. The solubility of the crystals was good in alcohol, acetone, acetic acid and ligroin (from the latter they separated in the form of lustrous, pinkish needles), moderate in ether, and poor in benzene. After recrystallization from aqueous alcohol, the very slightly pink needles melted at 104-105° without decomposition.

Found %: N 8.09, 8.44; equiv. 333, 331. $C_{14}H_{18}O_6N_2$. Calculated %: N 8.33; equiv. 335.

o-Carboxyphenylhydrazone of α-ketoglutaric acid (Table 2, 7a). 3.35 g ester (m.p. 104-105°) after saponification with 10% aqueous alcoholic solution of sodium hydroxide gave 2.52 g (80%) yellowish-pink crystals of the o-carboxyphenylhydrazone of α-ketoglutaric acid, melting at 220-222°. The crystals gave a positive Bülow reaction. The product was insoluble in water and very sparingly soluble in organic solvents (alcohol, ether, ethyl acetate, benzene, acetone).

After several precipitations with water from solution in acetic acid, the substance melted at 225° with decomposition.

Found %: N 9.87, 9.91; equiv. 94.5, 94.9. $C_{12}H_{12}O_6N_2$. Calculated %: N 10.00; equiv. 93.4.

The composition and structure of the compound were confirmed by transformation into an indole derivative which proved to be identical with the indole derivative prepared from the o-carboxyphenylhydrazone of diethyl-α-ketoglutarate.

p-Nitrophenylhydrazone of diethyl α-ketoglutarate (Table 2, 8). 6.90 g p-nitroaniline was diazotized and after removal of the hydrochloric acid with sodium acetate it was coupled with the sodium derivative of α-acetoglutaric ester prepared from 11.5 g ester, 1.15 g sodium and 30 ml alcohol absolute, cooled with ice and salt. 10% sodium hydroxide was stirred into the solution until neutral to litmus. Stirring was continued for an hour (until the diazo reaction was negative). The odor of ethyl acetate was given off. The dark-red oil was separated, washed with water and allowed to stand; it did not crystallize and was therefore heated for 10-15 minutes with 20 ml 10% alcoholic solution of hydrochloric acid. On cooling, the oil then formed a dark-red crystalline mass. The crystals were triturated in a mortar with a small amount of ethyl acetate, drained, and washed on the filter with small portions of ethyl acetate. Weight of crystals 14.54 g (87%). M.p. 131-134°. The solubility of the crystals was good in hot acetic acid and hot alcohol, moderate in ethyl acetate, poor in ether and benzene. After two recrystallizations from acetic acid and then from absolute alcohol, the bright-yellow, slender needlets of the p-nitrophenylhydrazone of diethyl α-ketoglutarate melted at 137° and did not give Bülow reaction.

Found %: N 12.31, 12.23. $C_{15}H_{19}O_6N_3$. Calculated %: N 12.46.

p-Sulfophenylhydrazone of α-ketoglutaric acid (trisodium salt; Table 2, 9). To 5.8 g sodium sulfanilate dissolved in 50 ml hot water was added 14 ml concentrated hydrochloric acid; portionwise addition was then made at −3° to the liquid, containing crystals of hydrochloride, of a solution of sodium nitrite (1.8 g nitrite in 8 ml water). At the expiration of 20 minutes, when the diazotization was complete, the crystals of diazosulfonate were quickly drained, washed with ice water, stirred into 50 ml cold water and introduced in small portions into the sodium derivative prepared from 5.75 g α-acetoglutaric ester, 0.57 g sodium and 15 ml absolute alcohol. After a period of 30 minutes from the start of the stirring in, the coupling was completed; the beaker contents consisted of a transparent, dark-red solution. This was filtered and evaporated on a water bath. The residue of viscous, red oil was stirred with 30 ml ethyl alcohol and sodium hydroxide (2 g in 8 ml water). Orange crystals of salt came down after a few minutes and were drained and dried. Weight 7.0 g. Evaporation of the filtrate gave another 2.1 g light-orange crystals. Hence the total yield was 9.1 g (95.3%). The solubility of the crystals is excellent in water, moderate in aqueous alcohol and nil in organic solvents (benzene, ligroin, ethyl acetate, acetone). The substance crystallized from aqueous alcohol in the form of yellow needlets with a tinge of pink, not containing water of crystallization and not giving the Bülow reaction. A test for sulfur gave a positive reaction.

Found %: N 7.02, 7.09; Na 17.65, 17.81. $C_{11}H_9O_7N_2SNa_3$. Calculated %: N 7.33; Na 18.06.

α-Naphthylhydrazone of α-acetoglutaric acid (Table 2, 10). A mixture of 2.86 g α-naphthylamine, 110 ml water and 12 ml concentrated hydrochloric acid in a porcelain beaker was gently heated (until all was dissolved) and then placed in a freezing mixture; at a temperature of 0 to +4° it was diazotized with sodium nitrite solution (1.4 g nitrite in 8 ml water). After 10 minutes from the completion of diazotization, addition was made to the diazo solution of the sodium compound prepared from 4.6 g α-acetoglutaric ester, 0.46 g sodium and 15 ml absolute alcohol. Dropwise addition was then made to the reaction mixture of a cooled 10% aqueous solution of sodium hydroxide until neutral to litmus. Coupling was completed in an hour. The red-violet oil was extracted with ether, the ether was distilled off and the residue of oil was saponified with 15% aqueous alcoholic solution of potassium hydroxide (25 ml). After heating for two hours, addition was made

to the flask of water, and the alcohol was distilled off. The cooled solution was extracted with ether to remove neutral impurities and the solution was then diluted 20 times with water, cooled and acidified with 5% hydrochloric acid. The brownish flocs of the α-naphthylhydrazone of α-ketoglutaric acid were washed on the filter with water and dried in a vacuum-desiccator (since they darkened in the air). Weight 2.7 g (47.2%), m.p. 153-158°.

The compound showed good solubility in acetic acid, alcohol, ethyl acetate and acetone; moderate solubility in ether in the cold; poor solubility in benzene and ligroin. When the amorphous, brownish powder was heated with acetic acid, it changed into crystals. The latter, however, were difficult to purify. Repeated recrystallization from glacial acetic acid and then from 50% alcohol with addition of carbon gave light-orange thin plates melting at 170° with decomposition. A green color was produced with potassium bichromate and strong sulfuric acid.

Found %: N 9.59, 9.54; equiv. 139, 141. $C_{15}H_{14}O_6N_2$. Calculated %: N 9.79; equiv. 143

β-Naphthylhydrazone of α-ketoglutaric acid (Table 2: 11). The diazo solution from 3.6 g β-naphthylamine, after elimination of excess hydrochloric acid with sodium acetate, was added to the sodium compound prepared from 5.75 g α-acetoglutaric ester. The viscous, bright-red oil resulting from coupling was saponified in conditions similar to those applied in the saponification of the azo ester from α-naphthylamine. Yield 2.4 g (33.1%) of the β-naphthylhydrazone of α-ketoglutaric acid in the form of a dark-colored, amorphous powder, decomposing at 140-144°. The product has good solubility in ethyl and methyl alcohols, ethyl acetate, acetic acid and acetone; moderate solubility in ligroin and hot benzene; poor solubility in ether. It is extremely difficult to purify, however. After repeated recrystallization from alcohol with addition of carbon, and then from acetic acid and ligroin, the β-naphthylhydrazone was in the form of a light-brown, amorphous powder, decomposing when heated to 150°.

Found %: N 9.53, 9.61; equiv. 138, 141. $C_{15}H_{14}O_6N_2$. Calculated %: N 9.79; equiv. 143.

Diethyl ester of α-(4-sulfonaphthyl-1-azo)-α-acetoglutaric acid (sodium salt: Table 2: 12). 5.6 g naphthionic acid was dissolved in aqueous sodium carbonate (2.8 g carbonate in 50 ml water). To the solution was added 12 ml concentrated hydrochloric acid (1.19) and, at −2°, a sodium nitrite solution (1.8 g nitrite in 8 ml water); a yellow paste of diazosulfonate was formed. This was drained, washed with ice water, mixed with 50 ml ice water and introduced, with rapid stirring, into a cooled (ice-salt) sodium compound prepared from 5.75 g α-acetoglutaric ester, 0.57 g sodium and 15 ml absolute alcohol.

Mixing of the solutions at first gave a reddish-orange emulsion which quickly disappeared; coupling was complete after 40 minutes. The reddish-brown, transparent liquid, containing the product of reaction, was filtered and evaporated on the water bath. Trituration of the residual reddish-brown oil with absolute alcohol caused the product to separate in the form of a dark-rose powder. Weight 9.3 g (78.5%). This product did not melt, it was moderately soluble on heating in ethyl alcohol (aqueous) and in methyl alcohol, readily soluble in water, insoluble in ethyl acetate, benzene, acetone and ligroin. It consisted of the sodium salt of the azo ester.

Found %: N 5.44, 5.68; Na 4.38, 4.32 $C_{21}H_{23}O_9N_2SNa$. Calculated %: N 5.76; Na 4.73.

4-Sulfonaphthyl-1-hydrazone of α-ketoglutaric acid (monopotassium salt, Table 2, 12a). 4.86 g of the above-described azo ester was heated for one hour on a water bath with 25 ml 20% alcoholic potash. After addition of water and removal of the alcohol, the cooled solution was acidified with dilute hydrochloric acid. Fine yellow, lustrous crystals came down after 5 minutes. Weight 3.7 g (91.4%). The substance has good solubility in acetic acid and poor solubility in acetone, benzene and ethyl acetate. After recrystallization from water (with carbon) and then from aqueous alcohol the 4-potassium sulfonaphthyl-1-hydrazone formed bright-yellow, infusible needles imparting a violet color to the nonluminous flame of a burner and leaving a mineral residue after burning. On carrying out the saponification with sodium hydroxide, the saponification product did not give a precipitate with hydrochloric acid. On the other hand, on adding to the alkaline solution, after saponification with sodium hydroxide, a solution of potassium hydroxide, a precipitate again failed to come down, but acidification of the latter solution with hydrochloric acid led to separation of the same lustrous, bronze-colored, scaly crystals of the monopotassium salt. The test for sulfur gave a positive reaction.

Found %: N 6.77, 6.63; K 9.41, 9.37; equiv. 197, 199. $C_{15}H_{13}O_7N_2SK$ Calculated %: N 6.91; K 9.65; equiv. 202.

II. β-Cyanoethylacetoacetic Ester — Some Products of Its Azo Coupling (Table 3)

The initial β-cyanoethylacetoacetic ester was synthesized in 77% yield by condensation of ethylacetoacetate with β-chloropropionitrile [29] and had the constants: b.p. (13 mm) 156°, (27 mm) 164-167°. d_{17}^{17} 1.0725; d_4^{17} 1.0705; $n_D^{17.5}$ 1.4474 MR_D 45.71; calculated for the keto form 45.37, for the enol form 46.42.

β-Cyanoethylacetoacetic ester was azocoupled with aniline and p-nitroaniline.

Phenylhydrazone of the ethyl ester of β-cyanomethylpyrotartaric acid (Table 3: 1). 9.3 g aniline was diazotized in the usual manner with sodium nitrite in presence of hydrochloric acid; the acid was removed by adding solid sodium acetate and the diazo solution was poured into β-cyanoethylacetoacetic ester (18.3 g) placed in a freezing mixture. With vigorous stirring, dropwise addition was then made from a dropping funnel of a cooled 10 % aqueous solution of sodium hydroxide until the reaction was neutral to litmus. The end of the reaction was signalized by the absence of free diazo compound (β-naphthol test) which usually required 40–60 minutes stirring. The dark-red oil was separated from the aqueous liquor, washed with water, stirred with 50 ml ethyl alcohol and left in an open beaker at room temperature. After 3 days it crystallized in dense, light-orange crystals, the crystallization process was accompanied by the separation (detected by odor) of acetic acid (cleavage of the CH_3CO group). The crystals of the phenylhydrazone of the ethyl ester of β-cyanomethylpyrotartaric acid were drained, washed with ether and dried. Weight 24.01 g (98%). After recrystallization from acetic acid, the pinky-yellow crystals melted at 159° and gave a positive Bulow reaction.

Found %: N 16.93, 16.99. $C_{15}H_{17}O_5N_3$. Calculated %: N 17.14. Keimatsu and Sugasawa, who were the first to prepare and describe this compound, report a m.p. of 155° [29]. With the aim, therefore, of obtaining fuller confirmation of the nature of the compound prepared by us as the phenylhydrazone of the ethyl ester of β-cyanomethylpyrotartaric acid, previously described by Keimatsu and Sugasawa, we saponified it and obtained the anticipated phenylhydrazone of α-ketoglutaric acid; we also subjected it to Fischer's indole ring-closure reaction and obtained the anticipated ethyl ester of 2-carbethoxyindolyl-3-acetic acid. Consequently conclusive evidence has been obtained that the compound melting at 159° is the phenylhydrazone of the ethyl ester of β-cyanomethylpyrotartaric acid.

2.45 g phenylhydrazone of the ethyl ester of β-cyanomethylpyrotartaric acid (m.p. 159°) was mixed with 20 ml aqueous 20% potassium hydroxide solution and refluxed on the water bath for 6 hours. The cooled alkaline solution was diluted with water and acidified with dilute hydrochloric acid. On standing in a freezing mixture, the dark-red crystals of the acid separated. Weight 1.4 g, m.p. 147-149°. After recrystallization from aqueous alcohol and then from ethyl acetate, the light-yellow crystals melted at 152-153° with decomposition. A mixture with our previous preparation of the phenylhydrazone of α-ketoglutaric acid (m.p. 152-153°) did not suffer a depression of melting point.

p-Nitrophenylhydrazone of the ethyl ester of β-cyanomethylpyrotartaric acid (Table 3: 2). 3.45 g p-nitroaniline was diazotized in the usual manner. The inorganic acid (HCl) was removed with sodium acetate, and the diazo solution was then introduced into the cooled sodium derivative of β-cyanoethylacetoacetic ester (4.6 g ester, 0.6 g Na and 20 ml absolute ethyl alcohol). Dropwise addition was made with stirring of a 10% aqueous solution of sodium hydroxide until neutral. The oil was extracted with ether, and after the lapse of two days when the solvent had evaporated, it crystallized in orange crystals; weight 7.1 g (98%), m.p. 154-156°; the solubility of the crystals is good in ethyl alcohol, acetic acid, ethyl acetate and acetone. After recrystallization from acetic acid and then from alcohol, the light-brown needles (in clusters) melted at 158°.

Found %: N 18.60, 18.58. $C_{15}H_{16}O_4N_4$. Calculated %: N 18.65.

III Ethyl Ester of γ,γ-Diacetobutyric Acid and Some Products of Its Azo Coupling

This ester was synthesized from ethyl β-chloropropionate and acetylacetone by the procedure of Marsch [30] as simplified by us. To some cooled sodium ethylate (11.5 g Na and 160 ml absolute alcohol), contained in a round-bottomed flask fitted with a reflux condenser, was added 150 g freshly distilled acetylacetone, followed a few minutes later by 68 g ethyl β-chloropropionate. The mixture was heated on a water bath for 2½ hours until the reaction was over (absence of alkaline reaction). After distilling off the alcohol the flask contents were agitated with 200 ml cold water; the reaction product (a yellow oil) was separated, the aqueous solution was extracted with ether and the extract added to the oil. The ethereal solution was dried with anhydrous sodium sulfate. After distilling off the solvent, the oil was fractionated in vacuum. A fraction was collected which boiled at 153-154° (19 mm) or at 178° (43 mm) or at 182° (48 mm) [30]. Yield of twice-distilled ester 67 g (67 %). The literature reports a 50% yield [30].

The so-prepared ethyl ester of γ,γ-diacetobutyric acid had the constants: d_{15}^{15} 1.0668; d_4^{16} 1.0657; n_D^{17} 1.4528. MR_D 50.44 calculated for the keto form 50.16; for the enol form 51.16.

Azo coupling of this ester was performed with aniline, o-, m- and p-toluidines and p-nitroaniline.

In the case of aniline and the three toluidines, the products of azo coupling —the γ-arylnydrazones of the ethyl ester of β-pyruvylpropionic acid (coupling takes place with cleavage of the acetyl group) —are amorphous and could only be characterized after saponification to the corresponding carboxylic acids (Table 3; 3 to 6); but in the case of p-nitroaniline the product of coupling —the γ-(p-nitrophenylhydrazone) of the ethyl ester of β-pyruvylpropionic acid —was crystalline with m.p. 132° (Table 3; 7).

In the conditions of Fischer's reaction, (heating with 50% sulfuric acid solution), these arylhydrazones apparently undergo closure of the indole ring in the normal manner: with separation of ammonium sulfate, there are formed water-insoluble, amorphous products whose purification and closer characterization, however, could not be undertaken by us.

γ-Phenylhydrazone of β-pyruvylpropionic acid (Table 3; 3). 4.7 g aniline was diazotized in the usual manner. The excess of hydrochloric acid was removed with solid sodium acetate; the diazo solution was gradually introduced into the sodium derivative of γ,γ-diacetobutyric acid ethyl ester (in a freezing mixture of snow and salt) prepared from 10 g ester, 1.15 g sodium and 20 ml absolute ethyl alcohol. When the solutions were mixed, a dark-red oil was formed and the odor of ethyl acetate was given off. The oil was saponified with 50 ml 10% alcoholic aqueous solution of sodium hydroxide by heating on the water bath for 30 minutes. After addition of water and distillation of the alcohol, the neutral impurities were extracted with ether and the cooled alkaline solution was acidified with dilute hydrochloric acid. The precipitated light-brown crystals were washed and kept in a desiccator. Weight 10.5 g (90.1%), m.p. 163-166° without decomposition. Very good solubility in ethyl and methyl alcohol, ethyl acetate and acetone; good solubility in acetic acid and ether; moderate solubility in hot ligroin and hot benzene. After 3 recrystallizations from ethyl alcohol, the light-yellow, slender needles melted at 173-174° and gave a pronounced Bulow reaction.

Found %: N 11.96, 11.84; equiv. 232, 231. $C_{13}H_{14}O_3N_2$. Calculated %: N 11.96; equiv. 234.

2.34 g phenylhydrazone with m.p. 173-174° was dissolved in 25 ml 50% alcoholic solution of sulfuric acid and refluxed for 20 hours (until the Bulow reaction was negative). The mixture darkened and toward the end of the reaction it had a dark-brown color. Under cooling, the precipitate of ammonium sulfate was drained off at the pump and the filtrate poured into ice water; the precipitated amorphous dark-brown indole derivative (weight 1.82 g) had excellent solubility in alcohol, ether, ethyl acetate and acetone; it was insoluble in benzene or petroleum ether. Repeated efforts to bring it into a chemically pure form were in vain.

γ-(o-, m-, p-Tolylhydrazones) of β-pyruvylpropionic acid (Table 3, 4 to 6). 2.7 g o-, m-, p-toluidines were diazotized as in the previously described case of aniline (hydrochloric acid eliminated with sodium acetate) and coupled (in each individual case) with the sodium derivative prepared from 5 g γ,γ-diacetobutyric ester, 2.3 g sodium (0.1 g-atom instead of 0.025 g-atom) and 50 ml absolute alcohol. When the solutions made contact, the odor of ethyl acetate was detected and a dark-red, viscous oil was formed. The oil was saponified by heating with 10 % aqueous alcoholic sodium hydroxide; the precipitated Na salt of the hydrazone-acid was separated (poor solubility in cold water), washed with alcohol, dissolved in warm water and acidified with 5% hydrochloric acid. In all cases yellow crystals with the same outward appearance came down, they had good solubility in acetic acid, methyl and ethyl alcohols, ethyl acetate, acetone, and ligroin when heated.

The o-isomer gave 4.5 g crystals (72.4%) with m.p. 145-147°. After recrystallization from ligroin and then from alcohol, the bright-yellow needles melted at 150° and gave a marked Bulow reaction.

Found %: N 11.16, 11.12; equiv. 246, 248. $C_{13}H_{16}O_3N_2$. Calculated %: N 11.29; equiv. 250.

The yield of crude product from m-toluidine was 5.3 g (85.5%) with m.p. 149-153°. After recrystallization from acetic acid or alcohol, the product was in the form of small, light-yellow needles and melted at 155°. Bulow reaction negative.

Found %: N 11.09, 11.21; equiv. 248.247. $C_{13}H_{16}O_3N_2$. Calculated %: N 11.29; equiv. 250.

p-Toluidine gave 5 g of product (80.6%) with m.p. 162-165°. After recrystallization from alcohol, the p-tolylhydrazone formed slender, yellow needles melting at 167° and negative to the Bulow reaction.

Found %: N 11.14, 11.07; equiv. 247, 244. $C_{13}H_{16}O_3N_2$. Calculated %: N 11.29, equiv. 250.

Attempts to cyclize these arylhydrazones to the indole derivatives by heating with alcoholic sulfuric acid, as indicated above, ended in failure due to the difficulty of purifying the reaction products which were assumed to be indole derivatives.

γ-(p-Nitrophenylhydrazone) of the ethyl ester of β-pyruvylpropionic acid (Table 3: 7). 3.45 g p-nitroaniline was diazotized in the usual manner, the hydrochloric acid was removed with sodium acetate. The cooled diazo solution was brought into a solution of 5 g γ,γ-diacetobutyric ester in 20 ml alcohol. Into the mixture, cooled externally with snow and salt, with rapid operation of the stirrer was introduced dropwise a 10% aqueous solution of sodium hydroxide until the reaction was neutral to litmus. Stirring was continued for an hour (until the diazo reaction was negative). The condensation product—a dark-red oil—was separated and washed with water; residual oil was extracted with ether and added to the main bulk. The ethereal solution was left to evaporate at room temperature. After two days the oil crystallized completely. The crystals were washed with ether and dried. Weight 6.0 g (84.6% of the theoretical), m.p. 126-130°. The solubility of the substance was good in acetic acid, ethyl acetate and ethyl and methyl alcohols, moderate in ligroin and benzene. After recrystallization from ethyl alcohol and then from ethyl acetate, the p-nitrophenylhydrazone of the ethyl ester of β-pyruvylpropionic acid formed orange needles melting at 132° without decomposition.

Found %: N 13.04, 12.96. $C_{24}H_{17}O_5N_5$. Calculated %: N 13.21.

The nitrophenylhydrazone (m.p. 132°) was heated with 50% alcoholic sulfuric acid and the ammonium sulfate precipitate was separated. The filtrate was poured into water and gave a brown, amorphous precipitate, readily soluble in the majority of organic solvents. It was impossible, however, to bring it into the chemically pure form.

Coupling of α-carbethoxyglutaric ester with phenyldiazonium (Table 3: 8). 2.32 g aniline was diazotized and brought into the cooled sodium derivative of α-carbethoxyglutaric ester (3.5 g ester, 0.58 g Na and 20 ml absolute alcohol). After stirring for ten minutes, dropwise addition was made of 10% NaOH solution until the reaction was weakly alkaline. Stirring was continued for 40-50 minutes. The dark-red oily product of coupling was saponified with 25% alcoholic potassium hydroxide for 20-24 hours. Water was then added and the alcohol distilled off. After removal of the ether and the neutral impurities, the solution was carefully acidified with dilute hydrochloric acid; the precipitated crystals were washed and dried. Weight 2.90 g (49.1%), m.p. 145-149°. After recrystallization from ethyl alcohol (with carbon), the light-yellow crystals of the phenylhydrazone of α-ketoglutaric acid melted at 152-153°, it did not depress the m.p. of a preparation obtained by azo coupling of α-acetoglutaric ester.

Found %: N 11.75, 11.68. $C_{11}H_{12}O_4N_2$. Calculated %: N 11.86.

SUMMARY

1. A study was made of the coupling of α-acetoglutaric, γ,γ-diacetobutyric, α-carbethoxyglutaric and β-cyanoethylacetoacetic esters with various aryldiazoniums, it was established that the reaction products are dark-red oily substances which in the majority of cases do not crystallize; they are azo esters which change into the aryldiazoniums when treated with caustic alkali.

2. The greatest activity in the coupling reactions is manifested by β-cyanoethylacetoacetic ester and α-acetoglutaric ester; considerations about the probable cause of this behavior are advanced.

3. Hydrolysis of the $>C-C<$ bond proceeds with maximum ease in the case of azo esters formed by the more active azo and diazo components.

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Received October 28, 1952

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CONDENSATION OF ar-1-METHOXYTETRAHYDRONAPHTHALENE WITH FATTY ACID CHLORIDES

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For the preparation of (ar-1-hydroxytetrahydronaphthyl-4)-alkyl ketones ($HOC_{10}H_{10}COR$; R = alkyl) one of us [1] previously made use of the Fries rearrangement of ar-1-acyltetralols; it was then found that the reaction yields a mixture of ar-1,2- and ar-1,4-hydroxy ketones in which the ar-1,2-isomer greatly predominates; with increasing size of the acyl residue, the yield of (ar-1-hydroxytetrahydronaphthyl-4)-alkyl ketones sharply decreases.

On the basis of literature data [2] it could be assumed that in the condensation of ar-1-alkoxytetrahydronaphthalenes with acid chlorides in presence of aluminum chloride, the acyl group would be directed preferentially to the 4-position of the ring, and this route would offer the possibility of preparing (ar-1-alkoxytetrahydronaphthyl-4)-alkyl ketones and from them the corresponding hydroxy ketones in satisfactory yield. In this investigation we carried out a series of experiments on the condensation of ar-1-methoxytetrahydronaphthalene with chlorides of various fatty acids (acetic, propionic, butyric and palmitic); in this work, in accordance with expectation, (ar-1-methoxytetrahydronaphthyl-4)-alkyl ketones were obtained in yields of 60-80% of the theoretical.

The reaction was conducted in nitrobenzene solution with cooling. Formation of the isomeric (ar-1-methoxytetrahydronaphthyl-2)-alkyl ketones was not observed. The reaction was accompanied by slight resinification of the materials with consequent reduction to some extent of the yield of ketones.

Difficulties were encountered in splitting off the methoxyl group from the prepared ketones. The application for this purpose of the usual methods of dealkylation (heating with hydrogen halides) led to resinification. Moreover the hydrolysis of the methoxyl group appeared to be accompanied by cleavage of the acyl group, for in some cases ar-1-tetralol was isolated from the resinous products.

The required objective was reached by heating the methoxy ketones with $AlCl_3$ in benzene solution, when (ar-1-hydroxytetrahydronaphthyl-4)-alkyl ketones were obtained in a yield of 55-80% of the theoretical. But even in these conditions, cleavage of the acyl group was sometimes observed.

The structure of the (ar-1-hydroxytetrahydronaphthyl-4-)-alkyl ketones prepared by this route, and consequently also of the initial methoxytetrahydronaphthyl-(alkyl ketones), was established by comparison of the hydroxy ketones with the (ar-1-hydroxytetrahydronaphthyl-4-)-alkyl ketones synthesized by the Fries reaction.

The physicochemical and chemical properties of the (hydroxytetrahydronaphthyl)-alkyl ketones prepared by the different methods proved to be identical and no depression was observed in the melting point of mixed specimens.

EXPERIMENTAL

Ar-1-methoxytetrahydronaphthalene was prepared by two methods: 1) By the action of dimethyl sulfate on ar-1-tetrahydronaphthol in an aqueous alkaline medium [2]; 2) by catalytic hydrogenation of 1-methoxynaphthalene in alcoholic solution in presence of Raney nickel at a pressure of 90-100 atm. and a temperature of 130° [3].

(Ar-1-methoxytetrahydronaphthyl-4)-methylketone

30 g ar-1-methoxytetrahydronaphthalene was dissolved in 240 ml nitrobenzene and addition made with cooling and stirring of 14.5 g acetyl chloride (2.5% excess). Into the obtained solution at 0° was stirred, over a period of one hour, 30 g $AlCl_3$ (50% excess). Stirring was continued for another 4 hours and the mass left for 24 hours at room temperature, after which the reaction mass was poured into a mixture of ice and hydrochloric acid. The nitrobenzene and ethereal solutions were combined, the ether was first distilled off, and then the nitrobenzene (with steam). The residue after distillation of the nitrobenzene was extracted several times with ether. The ether extract was washed with 5% sodium hydroxide, then with water, and dried with sodium sulfate. The ether was driven off and the residue distilled in vacuum; b.p. 147-148° at 3 mm. yield 26.1 g (82.6% of theory).

After a second distillation the b.p. was 152-153° at 5 mm. Yield 24.5 g (77.5% of theory).

3.479 mg substance: 9.755 mg CO_2; 2.498 mg H_2O. 4.444 mg substance: 12.364 mg CO_2; 3.121 mg H_2O. Found %: C 76.47, 75.87, H 8.03, 7.86. $C_{13}H_{16}O_2$. Calculated %: C 76.43; H 7.90.

(Ar-1-hydroxytetrahydronaphthyl-4)-methylketone

5 g (ar-1-methoxytetrahydronaphthyl-4)-methyl ketone was dissolved in 200 ml absolute benzene. To the benzene solution was added 10 g $AlCl_3$. The reaction liquid was heated on the water bath at the boil for 6 hours and then poured into dilute hydrochloric acid and ice. The benzene layer was separated. The aqueous layer was extracted with ether and the ether extract combined with the benzene solution. The ether-benzene solution was washed several times with 8% potassium hydroxide solution. The alkaline solution was acidified with hydrochloric acid (1:1). The precipitated hydroxy ketone was filtered off and washed with water; m.p. 154-155°. Yield 3.8 g (82.6% of theory).

A melting point test on the mixture of the prepared compound with a specimen of (ar-1-hydroxytetrahydronaphthyl-4)-methyl ketone prepared by the Fries method did not give a depression.

(Ar-1-methoxytetrahydronaphthyl-4)-ethylketone

80 g ar-1-methoxytetrahydronaphthalene was dissolved in 640 ml dry nitrobenzene and addition was made, with cooling and stirring, of 60 g propionyl chloride (30% excess). The obtained solution was cooled and addition was made, at 0°, and with stirring for one hour, of 75 g $AlCl_3$ (50% excess). Stirring was then continued for 4 hours, after which the mass was left at room temperature for 24 hours before being decomposed in the usual manner. The nitrobenzene layer was separated and the aqueous layer extracted with ether. The combined ethereal and nitrobenzene solutions were washed with 5% sodium hydroxide solution and then with water. The ether and nitrobenzene were distilled off the latter with steam. The residue was extracted with ether. The ethereal solution was dried with sodium sulfate, the ether distilled off, and the residue distilled in vacuum. B.p. 169-180° at 10 mm. Yield 28 g (7% of theory).

A second distillation gave b.p. 169-171° at 10 mm. Yield 26 g. The product crystallized on standing: m.p. 36-37°.

3.708 mg substance: 10.432 mg CO_2; 2.785 mg H_2O. Found %: C 76.72; H 8.40. $C_{14}H_{18}O_2$. Calculated %: C 77.02; H 8.31.

(Ar-1-hydroxytetrahydronaphthyl-4)-ethylketone

5.5 g (ar-1-methoxytetrahydronaphthyl-4)-ethylketone was dissolved in 100 ml benzene and 11 g $AlCl_3$ added; the reaction mass was heated for 5 hours at the boil. After cooling, the reaction mass was poured into a mixture of hydrochloric acid (1:1) and ice. The benzene layer was separated, and the aqueous layer extracted with ether. The ethereal and benzene solutions were combined, washed with water and shaken several times with 8% potassium hydroxide solution; the solution was then washed with water again. The aqueous solution was combined with the alkaline one and the aqueous-alkaline solution was acidified. The precipitate was filtered and dried. Yield 2.7 g (55% of theory); m.p. 152-153°.

No depression was observed in a melting point determination on a mixture of this compound with the (ar-1-hydroxytetrahydronaphthyl-4)-ethylketone prepared by the Fries rearrangement.

The ether-benzene solution was dried, the solvents were driven off and the residue distilled in vacuum. Yield 1.2 g with b.p. 118-120° at 15 mm. This b.p. is close to that of ar-1-methoxytetrahydronaphthalene.

Experiment on cleavage of the methoxyl group with aid of hydrogen bromide

2 g (ar-1-methoxytetrahydronaphthyl)-ethylketone, 60 ml glacial acetic acid, and 16 ml hydrogen bromide (48%) were heated at the boil for 3 hours, after which the reaction mass was poured on to ice and worked up with ether. The ether extract was washed several times with potassium hydroxide solution, the alkaline solution acidified, and the resultant precipitate filtered off. Yield 0.5 g with m.p. 63-65°.

No depression was observed in the mixed melting test with ar-tetrahydronaphthol.

Ar-(1-methoxytetrahydronaphthyl-4)-propylketone

Into a three-necked flask, fitted with a mechanical stirrer and a side tube, was introduced 21.6 g ar-1-methoxytetrahydronaphthalene dissolved in 180 ml dry nitrobenzene. To the solution, cooled with ice and stirred, was added 14 g butyryl chloride, followed by 22 g $AlCl_3$ in small portions over a period of 1½ hours. After all the $AlCl_3$ had been added, the stirring was continued for another 4 hours, and decomposition effected as usual. Further working-up was similar to that in the preceding experiments on the condensation of ar-1-methoxytetrahydronaphthalene with acid chlorides.

A substance with b.p. 184-186° at 13 mm was obtained; yield 20.8 g (67.9% of the theoretical). On cooling, the compound solidified to a buttery mass.

3.323 mg substance: 9.452 mg CO_2; 2.589 mg H_2O. Found %: C 77.57; H 8.71. $C_{15}H_{20}O_2$. Calculated %: C 77.55; H 8.68.

Ar-(1-hydroxytetrahydronaphthyl-4)-propyl ketone

11 g ar-1-methoxytetrahydronaphthyl-4 propylketone was dissolved in 20 ml benzene. The solution was added to a mixture of 22 g $AlCl_3$ and 180 ml benzene. The reaction mass was heated for 6 hours at the boiling point of benzene and then poured, with cooling, into a mixture of hydrochloric acid (1:1) and ice. The benzene layer was separated and the aqueous layer extracted with ether. The benzene and ether extracts were combined and the benzene and ether were distilled off. The residue was dissolved in a little ether and the ethereal solution washed several times with 5-7% potassium hydroxide solution. At first the alkaline layer was deeply colored. The ethereal solution was washed with water, the aqueous solution was added to the alkaline solution, and the whole acidified with hydrochloric acid (1:1). The precipitate was filtered. Yield 6.2 g (60.7% of the theoretical); m.p. 131-132°.

No depression was observed in the mixed melting test with a specimen of the hydroxytetrahydronaphthyl-propylketone prepared by the Fries rearrangement.

Ar-1-palmitoyl-1-methoxytetrahydronaphthalene

Palmityl chloride was prepared from palmitic acid and thionyl chloride; b.p. 178-179°.

Into a three-necked flask, fitted with a mechanical stirrer and side tube, were introduced 25.8 g ar-1-methoxytetrahydronaphthalene and 200 ml nitrobenzene. To the solution was added, with cooling, 15.2 g palmityl chloride, followed gradually by 26 g $AlCl_3$ in the course of an hour; the reaction mass was then stirred for another 4 hours and left to stand for 18-20 hours. The viscous dark-red solution was decomposed in the usual manner. Ether was added to facilitate separation of the layers. The ether-nitrobenzene layer was separated from the aqueous layer and washed with 8% KOH solution. The ether-nitrobenzene layer was transferred to a flask and the ether distilled off on a water bath, after which the nitrobenzene was distilled in steam. The residual oil was extracted with ether. The ether extract was washed with water and dried, and the residue distilled in vacuum. Two fractions were collected: 1) b.p. up to 220° at 0.15 mm. 2) b.p. 220-240° at 0.15 mm.

A second distillation yielded the following fractions: 1) b.p. 200-214° at 0.08 mm (12 g); 2) b.p. 214-216° at 0.08 mm (16 g).

The substance with b.p. 214-216° at 0.08 mm is the supposed ar-4-palmitoyl-1-methoxytetrahydronaphthalene, a light-yellow oil which solidified on cooling.

3.301 mg substance: 9.780 mg CO_2; 3.337 mg H_2O. Found %: C 80.88; H 11.31. $C_{27}H_{44}O_2$. Calculated %: C 80.95; H 11.07.

SUMMARY

1. Condensation of ar-1-methoxytetrahydronaphthalene with fatty acid chlorides in presence of $AlCl_3$ gives (ar-1-methoxytetrahydronaphthyl-4)-alkyl ketones in yields of 60-80% of the theoretical.

2. Dealkylation of (ar-1-methoxytetrahydronaphthyl-4) alkyl ketones gave compounds identical with the (ar-1-hydroxytetrahydronaphthyl-4)-alkyl ketones prepared by the Fries method. Yields were 55-80% of the theoretical.

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Received August 21, 1952

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DERIVATIVES OF 2,4-DIAMINO-1,3,5-TRIAZYLALKYLCARBOXYLIC ACIDS. I.

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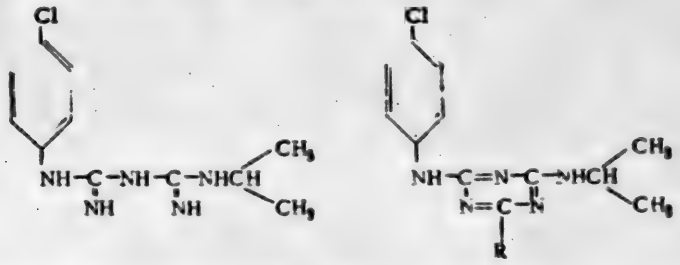
As far back as 1874, Nencki [1] established that the heating of guanidine salts of fatty acids leads to new compounds which he called guanamines. For example, on heating the guanidine salt of formic acid, formoguanamine is formed; the salt of acetic acid gives acetoguanamine, and so on. These compounds were accurately identified by Weith [2] and Claus [3] as derivatives of 2,4-diamino-1,3,5-triazine. Later Bamberger and Dieckmann [4] made a detailed study of this reaction and showed that the formation of guanamines proceeds through an intermediate biguanide. It was consequently established that derivatives of 2,4-diamino-1,3,5-triazines can be more conveniently prepared by starting from biguanides. In 1910 Rackmann [5] showed that biguanides have an extraordinarily high guanamine-forming tendency, formoguanamine being formed quantitatively by simple heating of free biguanide with an alcoholic solution of ethyl formate. The reaction proceeds similarly with benzoyl chloride. With dicarboxylic acids, however, the triazine ring does not close and the corresponding oxalyl-, malonyl-, succinyl-, etc. biguanides are formed.

A series of papers on the exploitation of the formation of 2,4-diamino-1,3,5-triazines was published by Ostrogovich and co-workers [6] who extended the reaction to nitriles, amides and amidines. It is interesting to note that Ostrogovich succeeded in extending this triazine ring closure reaction to acyl derivatives of biuret to form 2-aryl- or aralkyl-4,6-dihydroxy-1,3,5-triazines. Thus the tendency of the N–C–N–C–N grouping to form a six-membered ring is very great and even extends to oxygen-containing compounds.

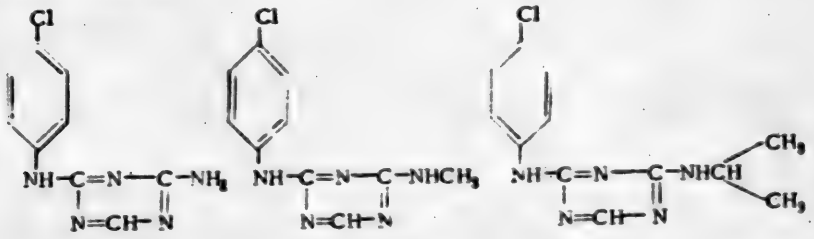
A series of patents have been published in recent years [7,8] which use this ability to biguanides to condense with various derivatives of esters containing groups such as –CN, –COOR, $-SO_3H$, $-NO_2$.

We were interested in derivatives of 2,4-diamino-1,3,5-triazine because of their structural similarity to biguanil (paludrine) or N'-p-chlorphenyl-N^5-isopropylbiguanide:



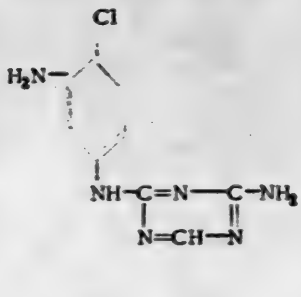
which is distinguished by high antimalarial activity. We undertook the synthesis of a group of triazine derivatives from biguanides by closure of the triazine ring with the objective of examining the effect of this closure on antimalarial activity.

Starting from the corresponding biguanides, V. N. Sokolova has prepared 2-amino-4-p-chlorophenylamino-1,3,5-triazine (I), 2-methylamino-4-p-chlorophenylamino-1,3,5-triazine (II), and 2-isopropylamino-4-p-chlorophenylamino-1,3,5-triazine (III):

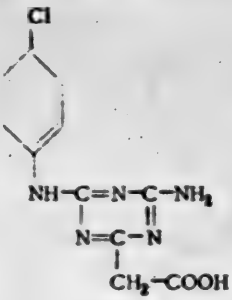


(I) (II) (III)

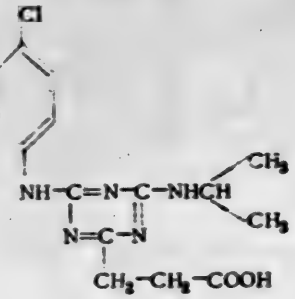
Since these compounds possessed weak antimalarial activity and were characterized by very poor solubility in water, while their salts were most unstable and suffered complete hydrolysis, we set ourselves the task of eliminating the solubility factor as a possible cause of the low activity by preparing compounds of the same type but exhibiting better solubility in water. Improved water solubility should be attainable by: 1) introduction of the amino group into the benzene ring and the preparation, from the resultant base, of stable salts. 2) introduction of alkylcarboxylic acid groups into the triazine ring and transformation of the acids into their salts. In the pursuit of our objective the compounds (IV), (V) and (VI) were synthesized:



(IV)



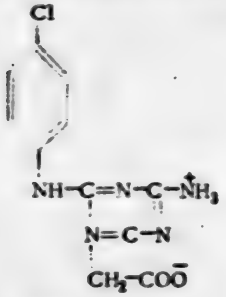
(V)



(VI)

2-Amino-4-(p-chloro-m-aminophenyl)-amino-1,3,5-triazine (IV) was prepared from 4-chloro-3-nitroaniline; the latter was obtained by the method of Claus and Stiebel [9], slightly modified by us. Reaction of 3-nitro-4-chloroaniline hydrochloride with dicyanodiamide in an aqueous medium in Cohn's conditions [10] gave p-chloro-m-nitrophenyl-biguanide in good yield. We effected the first of the two above-mentioned syntheses by reducing the nitro group to the amino group and cyclizing the p-chloro-m-aminobiguanide to the triazine with the help of ethyl formate. Experiments on catalytic reduction with skeletal nickel catalyst, however were unsuccessful. Although hydrogen absorption proceeded normally, the reduced compound resinified at extraordinary speed even in a nitrogen atmosphere and it was impossible to isolate a pure substance from the resin. We therefore decided to close the triazine ring in the first place and then to reduce the nitro group. Reaction of p-chloro-m-nitrophenyl-biguanide with ethyl formate in an alcoholic medium [5] gave 2-amino-4-(p-chloro-m-nitrophenyl)-amino-1,3,5-triazine, which by catalytic reduction with palladium-on-carbon gave 2-amino-4-(p-chloro-m-aminophenyl)-amino-1,3,5-triazine. This base was perfectly stable and its hydrochloride was readily soluble in water.

We realized the synthesis of 2-amino-4-(p-chlorophenyl)-amino-1,3,5-triazine-6-acetic acid (V) by starting from p-chlorophenyl-biguanide, prepared by the method of Strukov and coworkers [11]. After recrystallization from water, p-chlorophenylbiguanide melted at 96-97° and contained 1 mole water of crystallization. Its anhydrous form melted at 128-129° [12]. Condensation of p-chlorophenylbiguanide with ethyl cyanoacetate gave a good yield of 2-amino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-acetonitrile. Saponification of the nitrile proceeds with some difficulty. When heated with a large excess of 10% NaOH solution, the nitrile went into solution after 3 hours and the free acid was then separated in 90% yield. 2-Amino-4-(p-chlorophenyl)-1,3,5-triazyl-6-acetic acid is an inner salt and therefore has a very high melting point (326-327°). It may be represented by formula (Va).



(Va)

The synthesis of 2-isopropylamino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-propionic acid (VI) was effected by condensation of N^1-p-chlorophenyl-N^5-isopropyl-biguanide with the half ester acid chloride of succinic acid. Closure of the triazine ring proceeded through the acid chloride group and the reaction gave the ethyl ester of 2-isopropylamino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-propionic acid. Saponification of the ester with 4% alcoholic solution of NaOH gave 2-isopropylamino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-propionic acid.

Tests of the described new compounds for antimalarial activity were carried out in the chemotherapeutic department of our institute (Prof. G. N. Pershin) on strains of Plasmodium relictum and Plasmodium gallinaceum and did not reveal any active compounds among them.

EXPERIMENTAL

1. 4-Chloro-3-nitroaniline [9]. 100 g 4-chloroaniline was dissolved in 500 ml concentrated sulfuric acid and was nitrated (while cooling with ice and salt) with a mixture of 35 ml nitric acid (specific gravity 1.51) and 350 ml concentrated sulfuric acid. Nitration was conducted as quickly as possible at a temperature not exceeding 0°. The reaction mass was poured on to ice and neutralized with sodium carbonate. The precipitated 4-chloro-3-nitroaniline was purified by fractional crystallization from 10% methyl alcohol. Yield 79 g (58.5% of theory). M.p. 104-105°.

2. N-(4-Chloro-3-nitrophenyl) biguanide. a) A mixture of 10 g 4-chloro-3-nitroaniline, 5 g dicyanodiamide and 7 ml 30% hydrochloric acid was heated at the boil for 5½ hours on a glycerol bath [11]. The biguanide hydrochloride, which came down when the solution was cooled, was filtered off, washed with a little water and recrystallized from 30 ml water. Weight 12.8 g, m.p. 223-224.5°. The free base was isolated by adding a concentrated NaOH solution to the aqueous solution of the hydrochloride at 80-90°. Yield 11 g (74.7% of the theoretical). The m.p. depends on the speed of heating: at the rate of 2° per minute, the m.p. is 169-170°.

Biguanide base crystallizes with 1 molecule of water in the form of long prisms with an orange color. It loses water after prolonged drying at 100° and the color changes to yellow. It has good solubility in cold acetone, methyl and ethyl alcohols, ethyl acetate and glacial acetic acid; it is nearly insoluble in benzene, chloroform and petroleum ether.

0.1052 g substance: 4.12 ml 0.1 N HCl. Calculated: 4.08 ml 0.1 N HCl. 5.009 mg substance: 11.66 ml 0.01 g H_2SO_4. 5.167 mg substance: 12.24 ml 0.01 N H_2SO_4. Found %: N 32.59, 32.89. $C_8H_9O_2N_6Cl$. Calculated %: N 32.74.

3. 2-Amino-4-(p-chloro-m-nitrophenyl)-amino-1,3,5-triazine. 12.1 g N-(4-chloro-3-nitrophenyl)-biguanide was dissolved in 50 ml absolute alcohol and to the solution was added 4.5 ml ethyl formate. The solution was heated at the boil for 4½ hours. The precipitate was filtered, washed with alcohol, and recrystallized from 75% acetic acid. Yield 7 g (56% of the theoretical). Yellow powder, m.p. 274-275.5°, almost insoluble in water and organic solvents, soluble in glacial acetic acid.

4.822 mg substance: 10.72 ml 0.01 N H_2SO_4. 4.929 mg substance: 10.89 ml 0.01 N H_2SO_4. Found %: N 31.12, 30.93. $C_9H_7O_2N_6Cl$. Calculated %: N 31.52.

4. 2-Amino-4-(p-chloro-m-aminophenyl)-amino-1,3,5-triazine. 5.2 g 2-amino-4-(p-chloro-m-nitrophenyl)-amino-1,3,5-triazine in 110 ml 3.5% hydrochloric acid was reduced with hydrogen at room temperature in presence of palladium catalyst (0.05 g palladium chloride on 2 g active carbon) with mechanical shaking for 6 hours. 1,300 ml hydrogen was absorbed. The substance went into solution. The solution was filtered and evaporated to dryness in vacuum. The triazine hydrochloride (weight 5.3 g) was recrystallized from 20 ml water. The cream-colored powder, m.p. 255-257°, had good solubility in water.

0.1536 g substance: 9.4 ml 0.1 N NaOH. Calculated: 9.9 ml 0.1 N NaOH. 4.942 mg substance: 9.36 ml 0.01 N H_2SO_4. 5.178 mg substance: 9.81 ml 0.01 N H_2SO_4. 8.360 mg substance: 7.546 mg AgCl. 7.823 mg substance: 7.128 mg AgCl. Found %: N 26.52, 26.39; Cl 22.33, 22.53. $C_9H_9N_6Cl \cdot 2HCl$. Calculated %: N 27.14; Cl 22.94.

The free base was isolated by treatment of the aqueous solution of the hydrochloride with NaOH solution until weakly alkaline to litmus. It was purified by recrystallization from 50% ethyl alcohol. Yield 3.5 g (76% of the theoretical). The cream-colored powder melted at 248-249°, it dissolved in cold glacial acetic acid, hot ethyl alcohol, acetone and pyridine; insoluble in water, benzene, ether and chloroform.

5.264 mg substance: 13.32 ml 0.01 N H_2SO_4. 5.158 mg substance: 13.09 ml 0.01 N H_2SO_4. 7.688 mg substance: 4.580 mg AgCl. 8.203 mg substance: 4.805 mg AgCl. Found %: N 35.43, 35.53; Cl 14.74, 14.50. $C_9H_9N_6Cl$. Calculated %: N 35.52; Cl 15.01.

5. Formaldehyde-bisulfite derivative of 2-amino-4-(p-chloro-m-aminophenyl)-amino-1,3,5-triazine. A mixture of 5 g (1 mole) 2-amino-4-(p-chloro-m-aminophenyl)-amino-1,3,5-triazine, 3 g (1.05 moles) formaldehyde bisulfite compound, 50 ml alcohol and 5 ml water was heated with stirring at the boil for 20 hours. The precipitate was filtered off, washed with alcohol and recrystallized from water. Yield 3.5 g (46.9% of the theoretical). White powder, readily soluble in water, insoluble in organic solvents. Contains 1 mole of water of crystallization.

0.2078 g substance: 0.1283 g $BaSC_4$. Found %: S 8.47 $C_{19}H_{10}O_3N_6SNa \cdot H_2O$. Calculated %: S 8.63.

6. 2-Amino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-acetonitrile. 36.5 g N-(4-chlorophenyl)-biguanide (anhydrous with m.p. 128-129°) was dissolved in 120 ml absolute alcohol; to the solution was added 20 g ethylcyanoacetate. The mixture was heated at the boil in a flask under a reflux condenser for 2 hours. The yellow precipitate was filtered off, washed with alcohol and recrystallized from 50% alcohol. Yield 18 g (40% of the theoretical). Cream-colored plates with m.p. 225-226°, insoluble in water, soluble in alcohol and acetic acid.

5.014 mg substance: 11.44 ml 0.01 N H_2SO_4. 4.697 mg substance: 10.65 ml 0.01 N H_2SO_4.
Found %: N 31.94, 31.74. $C_{11}H_9N_5Cl$. Calculated %: N 32.24.

7. 2-Amino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-acetic acid. 10 g of the above-prepared 2-amino-4-(p-chloro phenyl) -amino-1,3,5-triazyl-6-acetonitrile in 195 ml 16% aqueous NaOH was heated at the boil for 3 hours. The precipitate gradually went into solution. The solution was cooled, filtered from turbidity and neutralized with hydrochloric acid (1:1). The triazylacetic acid was purified through the sodium salt. Yield 9.6 g (90% of the theoretical). Cream-colored powder with m.p. 326-327°. Insoluble in water and organic solvents; soluble in weak acids and alkalies.

2.529 mg substance: 4.42 ml 0.01 N H_2SO_4. 2.113 mg substance: 3.72 ml 0.01 N H_2SO_4.
Found %: N 24.47, 24.67. $C_{11}H_{10}N_5O_2Cl$. Calculated %: N 25.04.

8. Ethyl ester of 2-isopropylamino-4-(p -chlorophenyl)-amino-1,3,5-triazyl-6-propionic acid. To a mixture of 15 g N'-(4-chlorophenyl-N^5-isopropylbiguanide in 150 ml absolute toluene and 10.5 g anhydrous sodium carbonate was added dropwise, with energetic stirring, a solution of 13.5 g of the half ester acid chloride of succinic acid [13] in 100 ml absolute toluene at 65-70°. The temperature was gradually raised and was held at 110° for 20 hours (until disappearance of the biguanide reaction with ammoniacal copper sulfate solution). The solution was filtered hot from the precipitated sodium chloride. The filtrate solidified to a red-brown gel when cooled; it was carefully filtered from the toluene and to the residue was added weak hydrochloric acid and ether. With intense cooling, rubbing with a rod brought down crystals of the hydrochloride which were filtered off and repeatedly washed with ether. The hydrochloride was recrystallized from a mixture of 40 ml ethyl alcohol and 50 ml ether. Yield 10 g (50% of the theoretical). Needles with m.p. 165-166°, almost insoluble in water, insoluble in ether, soluble in alcohol.

4.163 mg substance: 7.914 mg CO_2; 2.207 mg H_2O. 3.584 mg substance: 4.47 ml 0.01 N H_2SO_4.
3.052 mg substance: 3.82 ml 0.01 N H_2SO_4. Found %: C 51.88; H 5.93; N 17.46, 17.59.
$C_{17}H_{22}O_2N_5Cl \cdot HCl$. Calculated %: C 50.99; H 5.75; N 17.50.

The ethyl ester of 2-isopropylamino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-propionic acid was isolated in the free state by treatment of the aqueous suspension of the hydrochloride with 17% NaOH solution in presence of ether. The mixture was shaken until the precipitate dissolved completely. The ether layer was separated and the ether distilled off. The residual oil was recrystallized from a little alcohol. Thin plates with m.p. 86-90°. Readily soluble in alcohol and ether; insoluble in water.

3.260 mg substance: 6.669 mg CO_2; 1.817 mg H_2O. 3.205 mg substance: 6.600 mg CO_2; 1.722 mg H_2O.
3.619 mg substance: 4.93 ml 0.01 N H_2SO_4. Found %: C 55.82, 56.19; H 6.23, 6.01; N 19.07.
$C_{17}H_{22}O_2N_5Cl$. Calculated %: C 56.12; H 6.05; N 19.25.

9. 2-Isopropylamino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-propionic acid. 3.75 g ethyl ester of 2-isopropylamino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-propionic acid hydrochloride was dissolved in 15 ml warm absolute alcohol, and to the solution was added 20 ml 4% alcoholic solution of NaOH. The precipitated sodium chloride was filtered off. The solution was heated on the water bath at the boiling point of alcohol for half an hour. The precipitate was filtered off and dissolved in 30 ml water, and the pure solution was acidified with dilute hydrochloric acid to a pH of 2. On standing, the precipitated gel formed crystals which were filtered off, dissolved in sodium bicarbonate solution and reprecipitated with dilute hydrochloric acid. The triazylpropionic acid was recrystallized from 30 times the amount of alcohol. Yield 2 g (63.7% of the theoretical). Needles with m.p. 216-218°, insoluble in water and acids; sparingly soluble in alcohol; soluble in bicarbonate solution.

0.1165 g substance. 3.51 ml 0 1 N NaOH. Calculated: 3.47 ml 0.1 N NaOH. 4.507 mg substance: 8.880 mg CO_2; 2.138 mg H_2O. 4.323 mg substance: 8.541 mg CO_2; 2.109 mg H_2O. 4.160 mg substance: 6.30 ml 0 01 N H_2SO_4. Found %: C 53.77, 53.92; H 5.31, 5.46; N 21.20. $C_{15}H_{15}O_2N_5Cl$. Calculated %: C 53.65; H 5.36; N 20.86.

10. 2-Isopropylamino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-propionic acid hydrazide. 2.3 g ethyl ester of 2-isopropylamino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-propionic acid hydrochloride was dissolved in 7 ml absolute alcohol, and to the solution was added 2 ml hydrazine hydrate. The solution was heated at the boil for an hour and left for 24 hours. The precipitate was filtered off, washed with alcohol and ether and recrystallized from 75% alcohol. Yield 1.7 g (85% of the theoretical). Needles, m.p. 168-170°. Insoluble in water and ether; soluble in alcohol.

4.219 mg substance: 7.950 mg CO_2; 2.110 mg H_2O 1.698 mg substance: 3.40 ml 0.01 N H_2SO_4. 1.801 mg substance: 3.60 ml 0.01 N H_2SO_4. Found %: C 51.42; H 5.59; N 28.02, 27.98. $C_{12}H_{19}ON_7Cl$. Calculated %: C 51.50; H 5.72; N 28.04.

SUMMARY

1. A series of 2,4-diamino-1,3,5-triazine derivatives was prepared by cyclization of the corresponding biguanide derivatives with esters of monobasic acids and the monoacid chlorides of dibasic acid half-esters. The latter method permitted direct preparation of the ester of a substituted 2,4-diamino-1,3,5-triazyl-6-alkylcarboxylic acid.

2. The following were synthesized: N-(4-chloro-3-nitrophenyl) biguanide 2-amino-4-(p-chloro-m-nitrophenyl)-amino-1,3,5-triazine, 2-amino-4-(p-chlorophenyl) amino-1,3,5-triazyl-6-acetonitrile the ethyl ester and hydrazide of 2-isopropyl-amino-4-(p-chlorophenyl) amino-1,3,5-triazyl-6-propionic acid 2,4-diamino-4-(p-chloro-m-aminophenyl)-amino-1,3,5-triazine, its formaldehyde bisulfite derivative and its hydrochloride 2-amino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-acetic acid, 2-isopropylamino-4-(p-chlorophenyl)-amino-1,3,5-triazyl-6-propionic acid.

The last four compounds proved to be inactive when tested for antimalarial action.

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Received November 3, 1952

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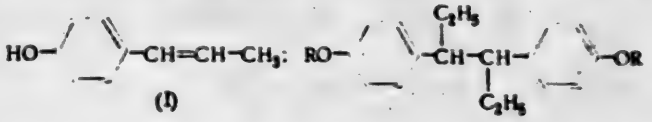
THE PROBLEM OF THE ESTROGENIC ACTIVITY OF ANOL DIMERS

II. SYNTHESIS OF THE ISOMERIC 3,5-DI-(p-HYDROXYPHENYL)-4-METHYLPENTENES

O. S. Madaeva, N. M. Goncharova and V. I. Maksimov

We have reported [1] that anol – p-propenylphenol (I) – is capable of transformation in various conditions into compounds possessing the properties of the male sexual hormone. It was shown that the liquid mixture of polymers formed on lengthy standing of the pure anol has an estrogenic activity of the order of 1 γ; that from the mixture of substances formed on demethylation of anethole with potassium hydroxide at 200-220° can be isolated a fraction that stimulates estrus in mice in a dose of 0.1-1 γ; and that a fraction with the same activity was obtained by vacuum-distillation of the resinous substances obtained by 2 hours' heating of anol at 230°.

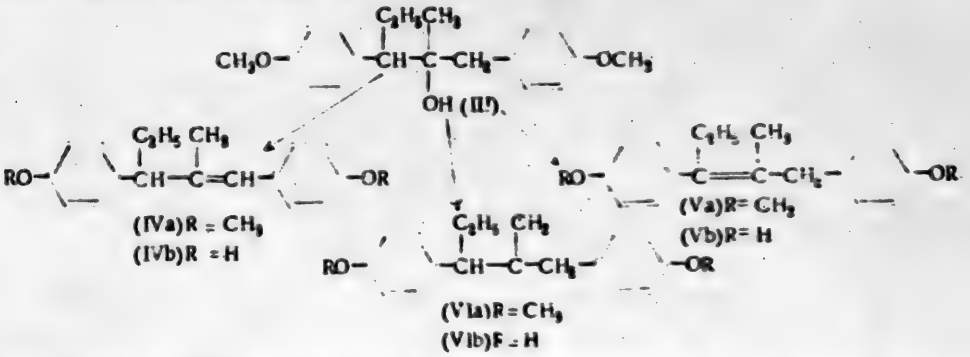


(I) (IIa) R = H (IIb) R = CH_3

We rejected the statements of Dodds and co-workers [2] that the estrogenic properties of compounds prepared by demethylation of anethole with potassium hydroxide are due to the presence in them of meso-3,4-di-(p-hydroxyphenyl)hexane (synestrol, IIa), and evidence was presented that the high estrogenic activity of substances formed from anol is due to some of its dimers – isomers of 3,5-di-(p-hydroxyphenyl)-4-methylpentenes. One of these dimers of anol – Δ_4-3,5-di-(p-hydroxyphenyl)-4-methylpentene (IV b) – was isolated by us from a mixture of polymers of anol in the pure crystalline form.

In further work on the fractionation of mixtures formed by polymerization of anol and on the separation from them of pure compounds, difficulties were encountered. We were unable to overcome these difficulties, and we therefore decided to attempt the synthetic preparation of the anol dimers of interest to us.

In this paper we describe an investigation of the dehydration of 3,5-di-(p-methoxyphenyl)-4-methylpentan-4-ol (III) and the preparation therefrom of the unsaturated compounds (IVa), (Va) and (VIa); we also studied the corresponding phenols (IVb), (Vb) and (VIb):

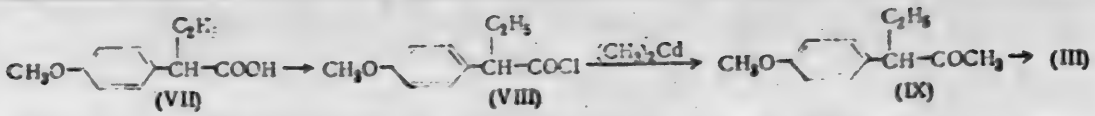


(IVa) R = CH_3 (IVb) R = H (Va) R = CH_3 (Vb) R = H (VIa) R = CH_3 (VIb) R = H

Two methods were used for preparation of the starting carbinol (III). In both of these we started from α-(p-methoxyphenyl)-butyric acid (VII), prepared from α-(phenyl) butyric acid via p-nitro-, p-amino and p-hydroxy-α-(phenyl)-butyric acid and methylation of the phenolic hydroxyl group of the latter with dimethyl sulfate.

In the first variant we attempted to prepare the carbinol (III) by the action of 3-(p-methoxyphenyl)-pentan-4-one [3] (IX) on p-methoxybenzyl magnesium bromide.

The ketone (IX) was synthesized by us from α-(p-methoxyphenyl)-butyryl chloride (VIII) and dimethylcadmium in 82.5% yield.



However, the reaction of p-methoxybenzyl magnesium bromide with (IX) does not proceed smoothly and carbinol (III) is formed in insignificant yield, in addition to which it is badly contaminated with dianisyl (side-product of the reaction of p-methoxybenzyl bromide with magnesium). This variant could not, therefore, be applied for preparative purposes. The prepared carbinol (III) was dehydrated by heating with iodine in xylene solution; oxidation of the formed mixture of unsaturated compounds with potassium permanganate in acetone [4] gave anisic acid; the neutral fraction of the oxidation products yielded a semicarbazone with m.p. 189° which did not depress the m.p. of 3-(p-methoxyphenyl)-pentan-4-one (IX) semicarbazone, which we also prepared by oxidation of isoanethole (IVa).

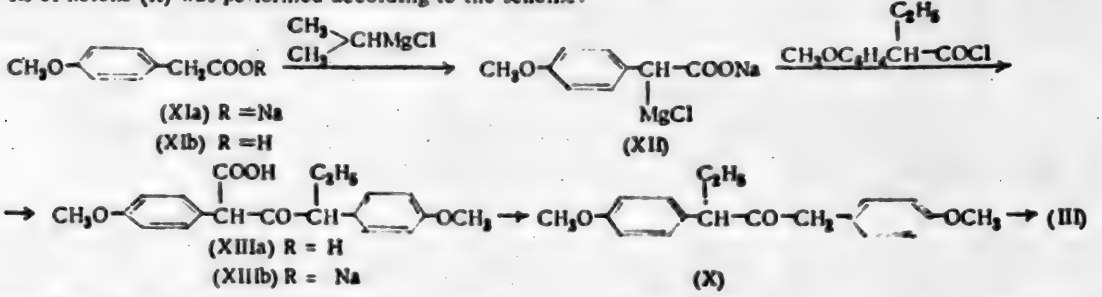
Formation of anisic acid and of ketone (IX) indicates that the main product of dehydration of carbinol (III) in these conditions was isoanethole (IVa).

The unsatisfactory yield of carbinol (III) and the difficulties of its purification prompted us to synthesize it by the other route from 3,5-di-(p-methoxyphenyl)-pentan-4-one (X) and methyl magnesium bromide.

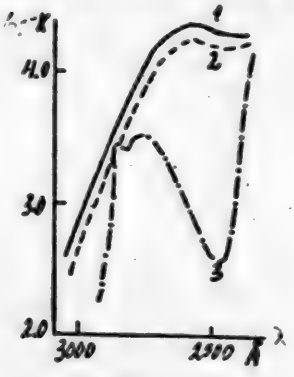
For the preparation of (X) we exploited the ability (discovered by Ivanov and co-workers [5]) of the sodium salt of phenylacetic acid to react with isopropyl magnesium bromide with formation of propane and the α-magnesium chloride derivative of phenylacetic acid.

The authors utilized this property for a series of reactions, including the preparation of alkylaromatic ketones.

We extended this reaction to the sodium salt of α-(p-methoxyphenyl)-acetic acid (XIa), and the synthesis of ketone (X) was performed according to the scheme:



The sodium salt (XIa) was prepared by neutralization of acid (XIb) with sodium carbonate in absolute alcohol solution; it was dried after distillation of the solvent in vacuum at 130° and was pulverized to a fine powder.



1 - Isoanethole; 2 - mixture of isomers; 3 - synestrol dimethyl ether.

The last traces of moisture were eliminated by distillation with absolute benzene; use was made in the reaction of a suspension of the sodium salt of α-(p-methoxyphenyl)-acetic acid in benzene. It was established that preparation of its magnesium halide salt in satisfactory yield necessitated the addition of the heated sodium salt of the acid in benzene at the instant of violent reaction of the magnesium with one-third of the required amount of isopropyl chloride; in these conditions propane at once begins to come off. The temperature of the reaction mass was held at 60° during addition of the remaining amount of isopropyl chloride, as well as afterwards until no more propane came off.

The condensation of (XII) with α-(p-methoxyphenyl)-butyryl chloride (VIII) and the subsequent decarboxylation of the keto acid (XIIIa) proceed smoothly and lead to the formation of 3,5-di-(p-methoxyphenyl)-pentan-4-one (X) in 48% yield. Reaction of (X) with methyl magnesium bromide gives a 98% yield of 3,5-di-(p-methoxyphenyl)-4-methylpentan-4-ol (III).

We effected the dehydration of the tertiary carbinol (III) by the method of A.P. Orekhov – boiling with acetyl chloride. The obtained mixture of 3,5-di-(p-methoxyphenyl)-4-methylpentenes was an oily, noncrystallizing mass.

Comparison of the ultraviolet absorption spectra of this mixture with the spectra of isoanethole and the dimethyl ether of synestrol (IIb) showed that the mixture does not contain isomer (VIa) [whose absorption spectrum must be of the same order as that of (IIb)]. Moreover, the possibility of formation of this isomer is very remote because A. P. Orekhov and co-workers [6, 7, 8] had shown that in the dehydration of tertiary carbinols of this series, the double bond is formed by cleavage of hydrogen from the less readily hydrogenated atom of carbon situated in the α-position to the phenyl radical.

The absorption spectrum of the prepared mixture (see diagram on previous page) was very similar to the absorption spectrum of isoanethole (IVa).

Oxidation of the mixture of 3,5-di-(p-methoxyphenyl)-4-methylpentenes in the conditions described for the oxidation of isoanethole [9] yielded, as main products, anisic acid and (from the neutral fraction) the semicarbazone of 3-(p-methoxyphenyl)-pentan-4-one (IX). From the recrystallization mother liquors of this semicarbazone was obtained only a very small quantity of a mixture of other semicarbazones. Evidently the dehydration of (III) leads mainly to formation of isoanethole (IVa).

Demethylation of the obtained mixture of unsaturated compounds with an alcoholic solution of KOH at 225-230° gave a light-yellow, resinous substance distilling at 190-193° (0.3 mm). On addition of benzene it partly crystallized. After recrystallization from benzene the precipitated product melted at 98-99° and did not give a depression with $\Delta_{4,5}$-3,5-di-(p-hydroxyphenyl)-4-methylpentene (IVb) prepared by demethylation of isoanethole in the same conditions. Its p-nitrobenzoate likewise did not give a depression with isoanol p-nitrobenzoate (m.p. 164°).

After separation of crystalline isoanol from the oily residue, which was undoubtedly a mixture, we were unable to isolate the individual substances.

Biological tests on the prepared mixture of 3,5-di-(p-hydroxyphenyl)-4-methylpentenes showed that it was capable of starting estrus in young mice after three injections under the skin in doses of up to 0.5γ in solution in peach oil. A most interesting and important fact is that the filtrate after separation of the crystalline isoanol (IVb) possessed an estrogenic activity of the order of 0.125-0.5γ. Isoanol (IVb), as we know, develops estrogenic activity only in doses of 100γ. Such a high activity of the obtained synthetic mixture of anol dimers – derivatives of 3,5-di-(p-hydroxyphenyl)-4-methylpentenes – confirms our previously expressed opinion that the latter are actually the cause of the estrogenic properties of the products of polymerization of anol.

EXPERIMENTAL

α-(p-Methoxyphenyl)-butyric acid (VII).

a) α-(p-Nitrophenyl)-butyric acid. A solution of 50 g α-phenylbutyric acid in 336 g sulfuric acid (sp. gr. 1.84) is nitrated with a mixture of 27.8 g nitric acid (sp. gr. 1.52) and 38.7 g sulfuric acid (sp. gr. 1.84) at +5°. On the following day the reaction mixture is poured into 305 g ice and the separated α-(p-nitrophenyl)-butyric acid is purified by recrystallization from twice the weight of 50% acetic acid. Yield 30 g (50% of the theoretical) of α-(p-nitrophenyl)-butyric acid with m.p. 120-122°.

b) α-(p-Aminophenyl)-butyric acid was prepared by reduction with hydrogen of α-(p-nitrophenyl)-butyric acid in presence of Raney nickel catalyst at 80° and an initial pressure of 30 atmospheres. Yield 78.3%, m.p. 138.5-140°.

c) α-(p-Hydroxyphenyl)-butyric acid. A solution of 35.8 g α-(p-aminophenyl)-butyric acid in a mixture of 58.8 g sulfuric acid (sp. gr. 1.84) and 160 ml water is diazotized with a solution of 15.2 g sodium nitrite in 40 ml water at +5°. The diazonium salt is decomposed by introducing it into a boiling solution of 720 g 8% sulfuric acid. Yield of α-(p-hydroxyphenyl)-butyric acid with m.p. 127-128° is 77.8% of the theoretical.

d) α-(p-Methoxyphenyl)-butyric acid (VII) was prepared by methylation of α-(p-hydroxyphenyl)-butyric acid with dimethyl sulfate in the conditions of Wilds and Biggerstoff [9], m.p. 65-67° after recrystallization from petroleum ether, yield 94% of theory.

p-Methoxyphenylacetic acid (XIb) is prepared from phenylacetonitrile through p-nitrobenzyl cyanide and p-nitrophenylacetic acid. Catalytic hydrogenation of the latter gives p-aminophenylacetic acid; this is diazotized and by the method of Carter and Hey [10] it is transformed into p-hydroxyphenylacetic acid which is methylated with dimethyl sulfate in the conditions described for compound (VII); (p-methoxyphenyl)-acetic acid melts at 83.5-84°.

3-(p-Methoxyphenyl)-pentan-4-one (IX)

α-(p-Methoxyphenyl)-butyryl chloride (VIII) was prepared by reaction of a benzene solution of α-(p-methoxyphenyl)-butyric acid with thionyl chloride. B.p. 133-135° at 10 mm.

A solution of methyl magnesium bromide is prepared from 4.8 g (0.2 mole) magnesium, 100 ml anhydrous ether and methyl bromide in a three-necked, round-bottomed flask of 250 ml capacity fitted with a reflux condenser, a stirrer, a mercury seal and a tube for passing through methyl bromide. Dimethylcadmium was prepared by rapidly adding to the ice-cooled methyl magnesium bromide solution 29.9 g (0.11 mole) cadmium bromide previously dehydrated by heating in a vacuum at 180-210° in a CO_2 stream. Stirring was then continued at room temperature until complete disappearance of the methyl magnesium bromide (negative reaction with Michler's ketone). To the formed organocadmium compound is added dropwise 21.2 g (0.1 mole) α-(p-methoxyphenyl)-butyryl chloride at such a speed that the reaction mass boils. After the whole of the chloride has been added, the mixture is heated for an hour at 40°. On the following day the reaction mass is decomposed with 5% sulfuric acid solution while cooling. The ethereal solution is separated and the aqueous layer is extracted with ether. The combined ether extracts are washed with 5% NaOH solution and dried with sodium sulfate; the solvent is distilled off. The residual oil is distilled in vacuum to give a fraction with b.p. 87-88° at 0.4 mm. Yield 82.4%. The semicarbazone, prepared by digesting (IX) with a solution of semicarbazide acetate, formed rhombic platelets (from alcohol), m.p. 187-188° (the literature gives 188-189° [3]).

The presence of a ketone group and the high degree of purity of the prepared ketone were established by determination of the oxime number by titration in presence of bromophenol blue. After the ketone had been boiled with hydroxylamine hydrochloride, the amount of released hydrochloric acid exactly corresponded to the weight of the ketone sample.

Determinations of nitrogen in the liquid oxime gave the following results:

8.525 mg substance: 0.332 ml N_2 (23°, 730 mm). Found %: N 4.32. $C_{19}H_{23}O_3N$. Calculated %: N 4.36.

3,5-Di-(p-Methoxyphenyl)-pentan-4-one (X)

a) Anhydrous sodium salt of (p-methoxyphenyl)-acetic acid. An alcoholic solution of 17.7 g (p-methoxyphenyl)-acetic acid is neutralized with 5.71 g sodium carbonate with heating. The solvent is evaporated in vacuum and the dry, hygroscopic residue of the sodium salt is finely pulverized and dried in a vacuum drying cupboard at 130°. The last traces of moisture are removed from the sodium salt by mixing with 60 ml absolute benzene and distilling off 30 ml benzene from the mixture.

b) 3,5-Di-(p-methoxyphenyl)-pentan-4-one is prepared in an apparatus consisting of a 250 ml three-necked flask fitted with a reflux condenser, stirrer, mercury seal and dropping funnel. The condenser is connected, via phosphorus pentoxide drying bottles, with a measuring cylinder filled with water for trapping the propane. To 4.43 g (0.184 mole) magnesium in 40 ml absolute ether is added a crystal of iodine and 1.73 g freshly distilled isopropyl chloride. After the start of the reaction, addition is made to the mixture of 80 ml absolute ether and (dropwise) 3.86 g isopropyl chloride; into the boiling reaction mass is rapidly introduced 20 g (0.106 mole) sodium (p-methoxyphenyl)-acetate in benzene. The bath temperature is raised to 55-60°; vigorous evolution of propane then commences and the gas is collected in the measuring cylinder. As soon as the gas evolution slows down, addition is made to the reaction mass of a further 8.76 g isopropyl chloride in 45 ml absolute ether over a period of 1½ - 2 hours. Heating at the specified temperature is continued until propane ceases to come off. If these conditions are observed, the magnesium halide complex is formed in a yield of about 70%, judging by the volume of propane collected. To the so-prepared reaction mass, containing the sodium salt of the magnesium halide compound of (p-methoxyphenyl)-acetic acid (XII), is added dropwise, while cooling with ice water and stirring, 22.47 g (0.106 mole) freshly distilled α-(p-methoxyphenyl)-butyryl chloride. Heat is developed. The mixture is boiled on the water bath for 3 hours. The resultant complex is decomposed by a 25% solution of ammonium chloride while being cooled. The resultant sodium salt of the ketocarboxylic acid (XIIIb) is decarboxylated by acidifying the reaction mass with sulfuric acid (acid reaction to Congo) and heating to boiling on the water bath for 2 hours. The ethereal solution is separated while cooling, and the aqueous layer is extracted with ether. The ether extracts are washed with 10% potassium hydroxide solution and with water and then dried with sodium sulfate; the solvent is then distilled off. Yield 22.2 g oily product. This is distilled in vacuum to give a fraction at 187-200° (2 mm). It partly crystallizes after standing for a long time in a refrigerator. The crystals are filtered, washed with alcohol and petroleum ether.

After recrystallization from alcohol, the m.p. is 51-52°; the yield of 3,5-di-(p-methoxyphenyl)-pentan-4-one is 47.8% of the theoretical.

3.35 mg substance: 9.336 mg CO_2; 2.168 mg H_2O. Found %: C 76.58; H 7.29. $C_{19}H_{22}O_3$. Calculated %: C 76.46; H 7.43.

This ketone does not give crystalline derivatives either with semicarbazone, hydroxylamine or m-dinitrophenylhydrazone.

3,5-Di-(p-Methoxyphenyl)-4-methylpentan-4-ol (III)

To an ice-cooled solution of methyl magnesium bromide, prepared from 1.17 g (0.049 mole) magnesium in 12 ml absolute ether, is added dropwise with stirring a solution of 5 g (0.017 mole), 3,5-di-(p-methoxyphenyl)-pentan-4-one in 30 ml absolute ether. The reaction mass is then boiled on the water bath for 2 hours. On the following day decomposition of the organomagnesium complex is effected under cooling with 25% ammonium chloride solution. After acidification with 20% sulfuric acid solution (to Congo), the aqueous layer is extracted with ether. The ether extracts are washed with water and dried with sodium sulfate and the ether is distilled off. Yield 5.1 g (98% of theory), of carbinol (III).

4.029 mg substance: 11.317 mg CO_2; 2.996 mg H_2O. Found %: C 76.60; H 8.31. $C_{20}H_{26}O_3$. Calculated %: C 76.38; H 8.33.

7.871 mg substance: 0.63 ml CH_4 (16.5°, 733 mm). Found %: OH 5.56. $C_{20}H_{26}O_3$ Calculated %: OH 5.41.

Dehydration of 3,5-di-(p-methoxyphenyl)-4-methylpentan-4-ol

5.1 g 3,5-di-(p-methoxyphenyl)-4-methylpentan-4-ol is heated with 4.7 g freshly distilled acetyl chloride on a water bath under a reflux condenser and calcium chloride tube until hydrogen chloride ceases to come off. The mixture is then poured on to ice and carefully neutralized with 10% NaOH solution. The separated oil is extracted with ether and the extract washed with water, dried with calcium chloride and distilled to remove the solvent. Vacuum fractionation of the oily residue (4.75 g), gave 3.4 g (71.5% of theory), of a light-yellow, mobile liquid with b.p. 186-187° at 0.6 mm. Its elementary analysis is consistent with a dimer of anol.

3.191 mg substance: 9.476 mg CO_2; 2.327 mg H_2O. Found %: C 80.99; H 8.16. $C_{20}H_{24}O_3$. Calculated %: C 81.03; H 8.16.

Oxidation of the products of dehydration of carbinol (III)

0.82 g of the substance with b.p. 186-187° at 0.6 mm was oxidized with potassium permanganate in acetone solution in the conditions described for the oxidation of isoanethole. 40% (0.32 g) of the starting substance was recovered unchanged. From the acid fraction of the oxidation products was separated a precipitate with m.p. 177-178° which did not give a depression with anisic acid (m.p. 179-180°). Treatment of the neutral products of oxidation with a solution of semicarbazide acetate gave a mixture of semicarbazones with m.p. 171.5-172°. After several recrystallizations from alcohol and benzene, a semicarbazone was isolated with m.p. 189° which did not give a depression with the semicarbazone of 3-(p-methoxyphenyl)-pentan-4-one prepared by oxidation of isoanethole.

Demethylation of products of dehydration of carbinol (III)

7.6 g potassium hydroxide, 3.4 g dehydration products of carbinol (III) and 19 g methanol are heated in an experimental autoclave at 225-230° for 24 hours. 10 ml methanol is then distilled off from the reaction mass, and to the residue is added 10 ml water with which the methanol residues are completely distilled off. The oily substance which separated from the aqueous-alkaline solution was extracted with ether. The aqueous-alkaline solution was diluted with 40 ml water prior to acidification with 20% sulfuric acid solution (to Congo). The resultant oil was extracted with ether after the usual working-up and the distillation of the ether, 1.95 g of a mixture of 3,5-di-(p-hydroxyphenyl)-4-methylpentenes (IVb, Vb, VIb) was obtained. Vacuum distillation gave a fraction with b.p. 190-193° at 0.2 mm. Yield 1 g.

5.153 mg substance: 15.174 mg CO_2; 3.492 mg H_2O. Found %: C 80.31; H 7.58. $C_{19}H_{24}O_3$. Calculated %: C 80.55; H 7.51.

On treating 0.6 g of the obtained fraction with benzene in the cold, it partly crystallized to give 0.15 g

crystals. After repeated recrystallization from benzene, the m.p. was 98-99°; the substance does not give a depression with 3,5-di-(p-hydroxyphenyl)-4-methylpentene (IVb) previously obtained by demethylation of isoanethole. The p-nitrobenzoate of this crystalline precipitate likewise does not depress the melting point of isoanol p-nitrobenzoate (m.p. 164°).

SUMMARY

1. The dehydration of 3,5-di-(p-methoxyphenyl)-4-methylpentan-4-ol was investigated.

2. A mixture of dimers of anol – isomeric 3,5-di-(p-hydroxyphenyl)-4-methylpentenes – was prepared by a synthetic route.

3. The structure of isoanol was confirmed by synthesis as $\Delta_{4,5}$-3,5-di-(p-hydroxyphenyl)-4-methylpentene.

4. It is shown that the prepared mixture of isomers of 3,5-di-(p-hydroxyphenyl)-4-methylpentene possesses a high estrogenic activity.

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Received August 24, 1952

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THE DIPOLE MOMENTS OF SOME FURAN AND THIOPHENE DERIVATIVES

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Following on our previously published [1] measurements of the dipole moments of some compounds of the furan and thiophene groups, we have now measured the dipole moments of 2-bromothiophene, 2,5-dibromothiophene, 5-bromo-2-nitrofuran and 5-nitro-2-furaldehyde.

All the measurements were made in benzene at 25° by the heterodyne method in an apparatus permitting simultaneous determination of the dielectric constant and the density of the solution.

The results of the measurements are presented in Table 1, where P_∞ is the total polarization at infinite dilution; R_D is the molar refraction for the sodium D line, calculated additively in cases 2, 3, and 4 and found experimentally for 2-bromothiophene; μ is the dipole moment.

TABLE 1

No	Substance	P_∞	R_D	$\mu \cdot 10^{18}$
1	2-Bromothiophene	72.34	33.62	1.36
2	2,5-Dibromothiophene	65.50	41.30	1.08
3	5-Bromo-2-nitrofuran	391.86	32.66	4.17
4	5-Nitro-2-furaldehyde	273.64	31.96	3.42

EXPERIMENTAL

We synthesized the investigated compounds by the literature methods. Purification of the solid compounds was effected by recrystallization until the melting points were constant. The liquid compounds were purified by repeated vacuum distillation. Dibromothiophene was synthesized twice and purified by two methods: five distillations in vacuum and conversion to the mercury compound which was fractionally crystallized from dioxane. The dibromothiophene then separating from the appropriate fraction was distilled in vacuum. The dipole moments of both specimens were measured and found to be identical.

The compounds had the following characteristics:

Benzene: Freezing point +5.5°; b.p. 80.12° ±0.01 at 760 mm.

2-Bromothiophene: B.p. 38.8-39.5° at 13.5 mm (the whole of the thread of the thermometer was immersed in the vapor); d_{4}^{20} 1.6284; n_D^{20} 1.5865; MR_D 33.62

2,5-Dibromothiophene: B.p. 56.5° at 1.5 mm (whole of thread in vapor). Freezes in dry ice and melts at −6°.

5-Bromo-2-nitrofuran: was recrystallized from petroleum ether; m.p. 48.0-48.35° (corr.).

5-Nitro-2-furaldehyde: was recrystallized from benzene, m.p. 34.6-35.1° (corr.).

The dielectric constants were measured in benzene at 25°. The total polarization was calculated by the method of Hedestrand [2]. Results are set out in Tables 2 to 5 where m denotes the concentration of the substance expressed in molar percentages; d is the density of the solution, ϵ is the dielectric constant. A, B, α and β are constants calculated by Hedestrand's method.

TABLE 2

2-Bromothiophene				2-Bromothiophene			
No.	m	d	ϵ	No	m	d	ϵ
0	0	0.87271	2.2714	0	0	0.87255	2.2714
1	0.3736	0.87601	2.2831	1	0.2771	0.87507	—
2	0.7559	0.87936	2.2927	2	0.3600	0.87581	2.2823
3	1.1303	0.88264	2.3042	3	0.5200	0.87710	2.2870
4	1.4988	0.88604	2.3155	4	0.6879	0.87877	2.2924
5	1.8567	0.88930	2.3263	5	0.8694	0.88032	2.2982
Extrap.	(1.9000)	(0.88960)	(2.3300)	Extrap.	(1.0000)	(0.88156)	(2.3020)
A = 0.34106; B = 14.7059;				A = 0.34110; B = 14.7087.			
α = 2.93; β = 0.889;				α = 3.06; β = 0.901;			
P_∞ = 71.00				Average P_∞ = 72.34		P_∞ = 73.11	

EVALUATION OF RESULTS

On comparing our experimental values for the dipole moments with the corresponding vectorial sums of the bond moments, we see that in the case of 2-bromothiophene ($\mu_{vect.}$ = 2.20) and 2,5-dibromothiophene ($\mu_{vect.}$ = 1.40) the moments are low, as had already been observed for 2-bromofuran and 2,5-dibromofuran [1].

TABLE 3

2,5-Dibromothiophene purified by distillation				2,5-Dibromothiophene purified through the mercury derivative			
No.	m	d	ε	No.	m	d	ε
0	0	0.87284	2.2714	0	0	0.87280	2.2714
1	0.0852	0.87419	2.2736	1	0.0820	0.87394	2.2733
2	0.3108	0.87781	2.2781	2	0.3149	0.87767	2.2781
3	0.4856	0.88068	2.2817	3	0.4859	0.88040	2.2815
4	0.6435	0.88312	2.2849	4	0.6633	0.88327	2.2852
5	0.8310	0.88608	2.2887	Extrap.	(1.0000)	(0.88861)	(2.2928)
Extrap.	(1.0000)	(0.88876)	(2.2929)				

A = 0.34101; B = 14.7037;
α = 2.150; β = 1.592;
P_∞ = 65.56.

A = 0.34107; B = 14.7061;
α = 2.140; β = 1.591;
P_∞ = 65.45

Average: P_∞ = 65.50

TABLE 4

5-Bromo-2-nitrofuran			
No.	m	d	ε
0	0	0.87266	2.2714
1	0.1793	0.87468	2.3150
2	0.2832	0.87587	2.3406
3	0.4114	0.87737	2.3721
4	0.5285	0.87877	2.4010
5	0.6631	0.88029	2.4342
Extrap.	(1.0000)	(0.88426)	(2.5174)

A = 0.34106; B = 14.7067;
α = 24.60; β = 1.160;
P_∞ = 391.86.

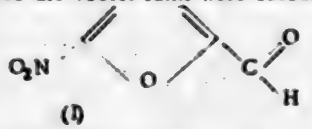
TABLE 5

5-Nitro-2-furaldehyde					
No.	m	d	ε	α	β
0	0	0.87273	2.2714	16.65	0.633
1	0.1201	0.87355	2.2915	16.74	0.633
2	0.2694	0.87443	2.3171	16.96	0.631
3	0.4201	0.87542	2.3432	17.09	0.640
4	0.5266	0.87604	2.3620	17.20	0.629

A = 34106. B = 14.7056.
P_∞ = 273.64.

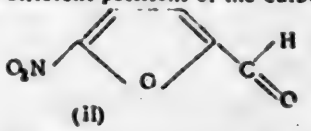
The moment of 5-bromo-2-nitrofuran is found to have a considerable exaltation ($\mu_{vect.}$ = 2.72, a difference of 1.45), i.e., in this case also, the nitro group brings about a considerable increase of the moment.

For nitrofuraldehyde the vector sums were calculated for two different positions of the carbonyl group:



(I)

and



(II)

In the case of (I) the vector sum is 1.11 D; in case (II) it is 4.31 D. The magnitude of the moment obtained by measurement (3.42 D) shows that internal rotation is here possible.

In all cases the vector sums were calculated with magnitudesof bond moments taken from aliphatic derivatives: μ_{C-Br} = 2.00 D; μ_{NO_2} = 3.40D; μ_{C-O} = 2.70 D. The moment of thiophene is 0.60 D; the moment of furan is 0.71 D. The angle at which the vectors are inclined to the ring moment is 78.5° for thiophene and 72° for furan.

SUMMARY

1. The dipole moments were measured of 2-bromothiophene(1.36 D), 2,5-dibromothiophene (1.08 D), 5-bromo-2-nitrofuran (4.17 D) and 5-nitro-2-furaldehyde (3.42 D).

2. The obtained magnitudes of the dipole moments were compared with the corresponding vector sums of the bond moments.

3. It is noteworthy that the dipole moments of bromo derivatives of thiophene are low in comparison with the

vector sum. The same observation was made for bromo derivatives of furan. The moment of 2-bromo-5-nitrofuran is low in relation to the vector sum. Internal rotation is possible in the case of 5-nitrofuraldehyde.

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Received July 11, 1952

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REACTION OF QUATERNARY SALTS OF HETEROCYCLIC BASES WITH AROMATIC NITROCHLORO COMPOUNDS

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A. I. Kiprianov and F. S. Babichev [1,2] found that methine bases of the thiazole series differ from the methine bases of other hetercyclic nitrogen compounds in reacting with alkyl halides, α-halodiketones and acid chlorides.

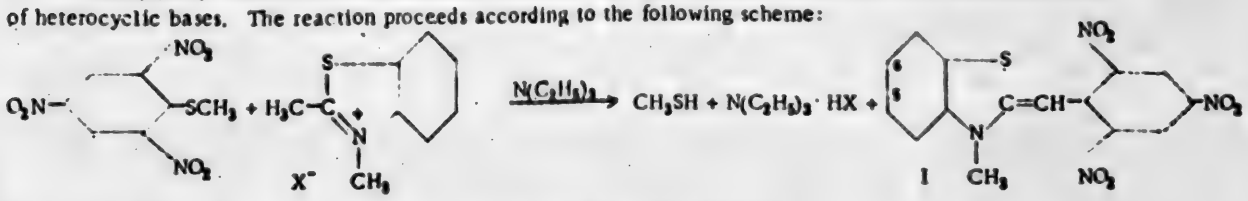
We were interested in establishing how methine bases of the thiazole series would react with picryl chloride and similar compounds.

Wizinger and Coenen [3] investigated the reaction of aromatic nitrochloro compounds with methine bases of the pseudoindole and quinaldine series. The reaction was performed by heating a mixture of the benzene solutions of the methine base and the aromatic nitrochloro compound and proceeded with formation of a deeply colored product; only half of the methine base enters into the condensation, the other half forming a quaternary salt.

We synthesized preparations 1 to 6 (see Experimental) and found that methine bases of the thiazole series react with picryl chloride in the above-described conditions in a similar manner to the quinaldine bases.

For the synthesis of such dyes, however, it is much more convenient to take the quaternary salt and to conduct the reaction in a medium of absolute alcohol in presence of triethylamine. In the majority of cases the dyes are then separated in the crystalline form. Yields for derivatives of thiazole and benzothiazole reach 80-90% of the theoretical.

Methylpicryl sulfide and trinitroanisole also enter into the condensation reaction with quaternary salts of heterocyclic bases. The reaction proceeds according to the following scheme:



The yields of dyes (I) in this reaction likewise reach 80-90% of the theoretical.

TABLE 1

I. R	Position of substituent	λ_{max} (in mμ) in benzene
H	–	552
NO_2	6	533
$N(CH_3)_2$	6	599
OCH_3	5	560
CF_3	5	535

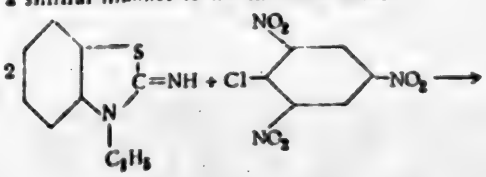
TABLE 2

IV. R	R'	λ_{max} (in mμ) in benzene	$E \cdot 10^{-4}$
CH_3	H	552	3
C_6H_5	H	554	–
CH_3	CH_3	605	1.25
CH_3	C_2H_5	605	–
C_2H_5	Cl	605	–
C_2H_5	CH_3	610	–

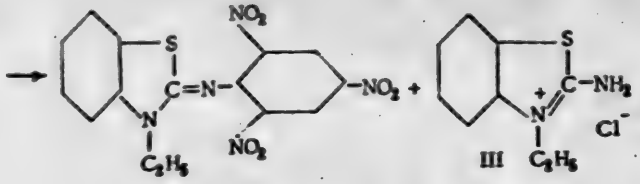
Applying these methods, we synthesized a series of preparations containing various substituents in the benzene ring of benzothiazole. Introduction of electropositive substituents brings about a shift of the absorption maximum in the direction of long waves, while electronegative substituents cause a shift in the short-wave direction. This is seen from Table 1.

In addition to picryl chloride, we condensed dinitrochlorobenzene and 3,5-dinitro-4-chlorobenzotrifluoride with 3-methyl-2-methylenebenzothiazoline. The absorption maxima of the dyes prepared from these compounds (see Experimental, preparations 4 and 5) are shifted in the short-wave direction by comparison with the preparation derived from picryl chloride.

N-Ethylbenzothiazoloneimine (II) reacts with picryl chloride in a similar manner to the methine bases:



II



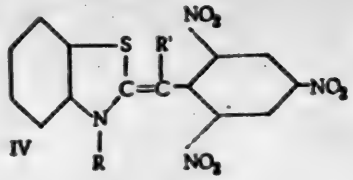
III

The absorption maximum of the dye (III) so obtained is shifted 100 mμ in the direction of the short waves in relation to preparation I.

Wizinger and Coenen [3] observe that methine bases containing substituents in the methylene group are incapable of reaction with picryl chloride.

We found, however, that methine bases and quaternary salts of 2-ethylbenzothiazole and 2-ethylbenzoselenazole react with picryl chloride. Also capable of condensation with picryl chloride are quaternary salts of 2-chloromethyl- and 2-n-propylbenzothiazole.

It is interesting that the resultant preparations (IV):



IV

have a considerably deeper color than compounds in which R'=H, as shown in Table 2.

Preparations in which R'=H have a reddish-violet color; replacement of the hydrogen of the methine group by CH_3, C_2H_5 and Cl leads to compounds with a dark-blue color.

The cause of such a sharp color change of the dyes is evidently the development of steric hindrances which make the molecules of the dye noncoplanar.

It is interesting that in the case of preparations in which R' = Cl, CH_3 or C_2H_5, the absorption maxima are identical. Unlike the salt-forming polymethine dyes investigated by A. I. Kiprianov and I. K. Ushenko [4, 5] which are characterized by steric hindrance, the preparations described in the present paper are nonsalt-forming.

Compounds containing substituents in the methine group possess a lower molecular extinction, are much more easily decolorized in light, and have a lower m.p. than unsubstituted dyes. These properties are characteristic of preparations possessing a noncoplanar structure [6].

The authors express their profound thanks to Prof. A. I. Kiprianov for valuable observations and advice.

EXPERIMENTAL

2-Chloromethylbenzothiazole ethochloride

A solution of 3 g N-ethyl-o-aminothiophenol in 5 ml benzene was poured dropwise into a solution of 3.6 g chloroacetyl chloride in 4 ml benzene with cooling and stirring. The bottom layer of oil was washed with benzene and ether and allowed to stand in a vacuum desiccator. After 4 hours the oil had solidified. Yield of crude, washed product 3.3 g or 70% of theory. The salt was purified by crystallization from a mixture of alcohol and ether. White needles, m.p. 169-172° with decomposition.

Found %: Cl 28.33, 28.37. $C_{12}H_{13}NSCl_2$. Calculated %: Cl 28.62.

Synthesis of Dyes

1. 3-Methyl-2-trinitrophenyl-methylenebenzothiazoline

This preparation was synthesized by four methods for comparison.

a) 0.9 g of 2-methylbenzothiazole methylmethosulfate was dissolved in 10 ml water and mixed in a separating funnel with 15 ml benzene and 0.6 g solid NaOH. The mixture was agitated, the benzene solution of the methine base was separated and dried for a short time with anhydrous Na_2SO_4, and then a solution of 0.4 g picryl chloride in 10 ml benzene was added to it. The mixture was heated for an hour on the water bath. The quaternary salt was filtered off and the benzene solution was concentrated. The dye that separated on cooling

was crystallized from benzene with addition of ether. Greenish prisms melting at 202-203° with decomposition.* λ_{max} in benzene 552 mμ. Yield 0.25 g or 42% of the theoretical.** $E \cdot 10^{-4}$ 3.

Found*** %: N 14.83, 14.78. $C_{15}H_{10}O_6N_4S$. Calculated %: N 14.97.

b) 0.25 g 2-methylbenzothiazole methylmethosulfate and 0.22 g picryl chloride were dissolved in 5 ml absolute alcohol by heating. Into the mixture was stirred a solution of 0.2 g triethylamine in 2 ml alcohol. The mixture was allowed to stand for 10 minutes and then cooled. The dye was filtered, washed repeatedly with water, alcohol and ether and dried in a vacuum-desiccator. M.p. 201-202° with decomposition. A mixed sample with the preparation obtained by method a) did not give a m.p. depression. Yield 0.3 g or 88% of theory.

c) 0.25 g 2-methylbenzothiazole methylmethosulfate, 0.24 g methylpicryl sulfide [7] and 0.2 g triethylamine were mixed and treated as in method b). During the reaction the mercaptan separated. Yield of washed product 0.28 g or 82.3% of theory. M.p. 200-201° with decomposition. No depression in mixed m.p. test with the preparation obtained by method a).

d) 0.5 g 2-methylbenzothiazole methylmethosulfate, 0.23 g trinitroanisole and 0.2 g triethylamine were mixed and treated as for method b). The yield of washed product was 0.27 g or 79.4% of theory. M.p. 199-200° with decomposition. A mixture with the preparation obtained by method a) did not show a m.p. depression.

2. 3-Methyl-6-nitro-2-trinitrophenyl-methylenebenzothiazoline

0.5 g 3-methyl-6-nitro-2-methylenebenzothiazoline [1] was dissolved in 20 ml nitrobenzene and a solution of 0.3 g picryl chloride in 10 ml nitrobenzene was added. The mixture was heated for 1½ hours on the water bath. The quaternary salt was filtered off, and from the nitrobenzene solution a dye was crystallized in the form of greenish-black prisms with a metallic luster. After washing with water, alcohol and ether the m.p. was 215° with decomposition. λ_{max} in benzene 533 mμ. Yield 0.32 g or 64% of the theoretical.

Found %: N 16.63. $C_{15}H_9O_8N_5S$. Calculated %: N 16.70.

3. 3-Methyl-2-trinitrophenylmethylene-α-naphthothiazoline

A solution of 0.7 g 3-methyl-2-methylene-α-naphthothiazoline [1] in 20 ml benzene was mixed with a solution of 0.4 g picryl chloride in 10 ml benzene and heated for an hour on the water bath. The product after evaporation of the benzene solution was crystallized from toluene. Black crystals. Yield 0.38 g or 56% of theory. λ_{max} in benzene 569 mμ. M.p. 207-208° with decomposition.

Found %: N 13.29. $C_{19}H_{12}O_6N_4S$. Calculated %: N 13.52.

4. 3-Methyl-2-(2',4'-dinitrophenyl)-methylenebenzothiazoline

A solution of 3-methyl-2-methylenebenzothiazoline (prepared from 1.1 g 2-methylbenzothiazole methylmethosulfate) in 15 ml benzene and 0.4 g 2,4-dinitrochlorobenzene in 8 ml benzene was boiled on the water bath for 3 hours. The quaternary salt was filtered off and the benzene solution was concentrated. The dye that came down on cooling was crystallized from benzene. Black needles with m.p. 243-244° with decomposition λ_{max} 502 mμ. Yield 0.19 g or 29% of the theoretical.

Found %: N 12.50. $C_{15}H_{11}O_4N_3S$. Calculated %: N 12.76.

5. 3-Methyl-2-(2',6'-dinitro-4'-trifluoromethylphenyl)-methylenebenzothiazoline

A solution of 3-methyl-2-methylenebenzothiazoline (prepared from 1.1 g 2-methylbenzothiazole methylmethosulfate) in 15 ml benzene and 0.54 g 3,5-dinitro-4-chlorobenzotrifluoride in 8 ml benzene were boiled on the water bath for 2½ hours. The dye that separated after evaporation of the benzene solution was crystallized from a mixture of benzene and ether. Black needles, m.p. 195-196°; λ_{max} 510 mμ. Yield 0.27 g or 35% of the theoretical.

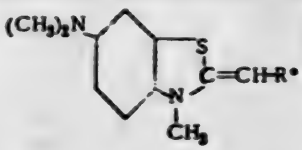
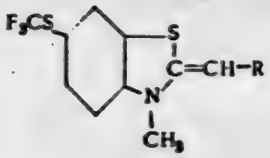
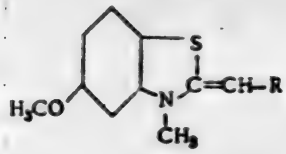
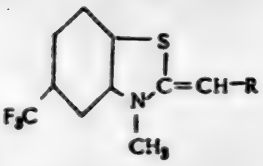
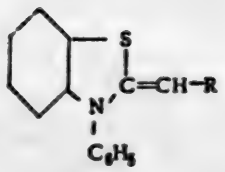
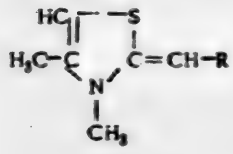
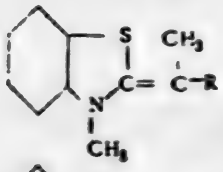
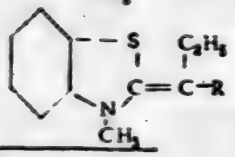
Found %: N 10.33. $C_{16}H_{10}O_4N_3SF_3$. Calculated %: N 10.56.

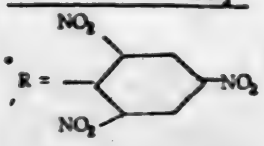
* All the dyes described in this paper are readily soluble in benzene, less soluble in chloroform and dichloroethane, poorly soluble in ether and almost insoluble in alcohol.

** The yields of dyes are calculated on the picryl chloride.

*** Before analysis all the preparations were dried in vacuum for 2 hours at 80°.

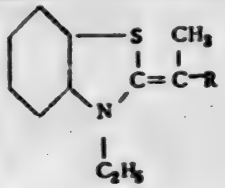
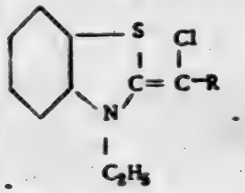
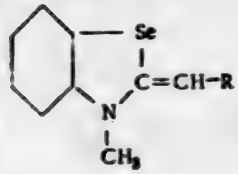
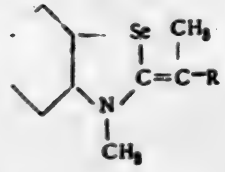
TABLE 3

Prep. No.	Formula of dye	Amount of quaternary salt (in g)	Aromatic nitro compound (g)	Method of prep.	Condensation: Amt. of abs. alcohol (ml)
1	2	3	4	5	6
7		Amount of quaternary salt (in g) 0.28	Methyl-picryl sulfide 0.22	1-c	10
8		2-Methyl-6-trifluoromethylmercaptobenzothiazole methoiodide 0.13	Picryl chloride 0.08	1-b	5
9		2-Methyl-5-methoxybenzothiazole methylmethosulfate 0.15	Picryl chloride 0.12	1-b	5
10		2-Methyl-5-trifluoromethylbenzothiazole methoiodide 0.2	Methyl-picryl sulfide 0.15	1-c	5
11		2-Methylbenzothiazole phenoiodide 0.25	Methyl-picryl sulfide 0.18	1-c	12
12		2,4-Dimethylthiazole methylmethosulfate 0.48	Picryl chloride 0.5	1-b	15
13		2-Ethylbenzothiazole methylmethosulfate 0.86	Picryl chloride 0.74	1-b	20
14		2-Propylbenzothiazole 0.37	Picryl chloride 0.3	1-b	10

* R = 

conditions		Solvent for crystallization	Yield (%)	Appearance	$\lambda_{max.}$ (mμ) in benzene	M.p. with decomp.	Analysis		
$N(C_2H_5)_3$ (g)	Duration of heating (min)						Found % N	Calculated Empirical formula	% N
7	8	9	10	11	12	13	14	15	16
0.2	5	Mixture of benzene and ether	81	Black crystals	599	206-207	16.85	$C_{17}H_{15}O_6N_5S$	16.78
0.07	2	Alcohol	78	Bronze crystals	550	201-202	11.56	$C_{16}H_9O_6N_4S_2F_3$	11.81
0.1	2	Benzene	81	Green crystals	560	201-202	13.79	$C_{16}H_{12}O_7N_4S$	13.86
0.15	5	Mixture of benzene and ether	83	Bronze needles	535	209-210	12.81	$C_{16}H_9O_6N_4SF_3$	12.67
0.2	5	Benzene	79	Black crystals	554	204-205	12.64 12.62	$C_{18}H_{12}O_6N_4S$	12.84
0.4	3	Benzene	82	Green crystals	550	189-190	16.57	$C_{12}H_{16}O_6N_4S$	16.76
0.6	2	Benzene	83	Violet crystals	605	155-156	14.36 14.28	$C_{18}H_{14}O_6N_4S$	14.43
0.25	2	Benzene	86	Violet crystals	605	153-154	13.75	$C_{17}H_{14}O_6N_4S$	13.93

TABLE 3 (Continued)

1	2	3	4	5	6
15		2-Ethylbenzothiazole ethoiodide 0.32	Picryl chloride 0.25	1-b	15
16		2-Chloromethylbenzothiazole ethochloride 0.3	Picryl chloride 0.3	1-b	10
17		2-Methylbenzoselenoazole methylmethosulfate* 0.24	Picryl chloride 0.25	1-b	10
18		2-Ethylbenzoselenazole methylmethosulfate*	Picryl chloride 0.22	1-b	10

* The authors thank F. S. Babichev for putting the quaternary salts of benzoselenazole at their disposal.

6. 3-Ethyl-2-trinitrophenylbenzothiazoloneimine

A solution of 0.6 g 3-ethylbenzothiazoloneimine in 15 ml benzene and 0.42 g picryl chloride in 8 ml benzene was boiled on the water bath for an hour. The precipitated 2-aminobenzothiazole ethochloride was filtered off, and the benzene solution was concentrated. The dye that came down on cooling was crystallized from benzene. Stout yellow crystals with m.p. 194°; λ_{max} 430 mμ. Yield 0.4 g or 61.5% of the theoretical.

Found %: N 17.86, 17.77. $C_{15}H_{11}O_6N_5S$. Calculated %: N 17.99.

All the remaining dyes were prepared not from the methine bases but directly from the quaternary bases as for preparation 1 by methods b) or c).

The conditions of their preparation and their properties are presented in Table 3. All the compounds were analyzed for nitrogen with exception of preparation 16, in which the chlorine was determined.

SUMMARY

1. 18 dyes were synthesized by condensation of the methine bases and quaternary salts of heterocyclic bases with aromatic nitrochloro compounds.

2. It is shown that methylpicryl sulfide and trinitroanisole enter into the condensation reaction with quaternary salts of heterocyclic bases.

7	8	9	10	11	12	13	14	15	16
0.2	2	Benzene	82	Violet needles	610	151-152	13.72 13.75	$C_{17}H_{14}O_6N_4S$	13.93
0.24	2	Mixture of benzene and ether	60	Black crystals	605	145-147	8.15 8.28 (Cl)	$C_{16}H_{11}O_6N_4SCl$	8.42 (Cl)
0.2	2	Washed with hot alcohol; crystallization from benzene	45	Black crystals	560	202-203	13.01	$C_{15}H_{10}O_6N_4Se$	13.29
0.2	2	Washed with hot alcohol; crystallization from benzene	39	Black crystals	605	155-156	12.58	$C_{16}H_{12}O_6N_4Se$	12.87

3. Introduction into the benzene ring of benzothiazole of electropositive substituents causes a shift of the absorption maximum of the dye in the long-wave direction; introduction of electronegative substituents shifts the absorption maximum toward shorter wave lengths.

4. Replacement of the hydrogen in the methylene group of a dye by CH_3, C_2H_5 and Cl leads to a marked deepening of color. This color change is evidently due to steric hindrance which renders the molecule of the dye noncoplanar.

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Received July 8, 1952

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* See Consultants Bureau translation, p. 149.

** See Consultants Bureau translation, p. 1971.

*** See Consultants Bureau translation, p. 139.

**** See Consultants Bureau translation, p. 543.

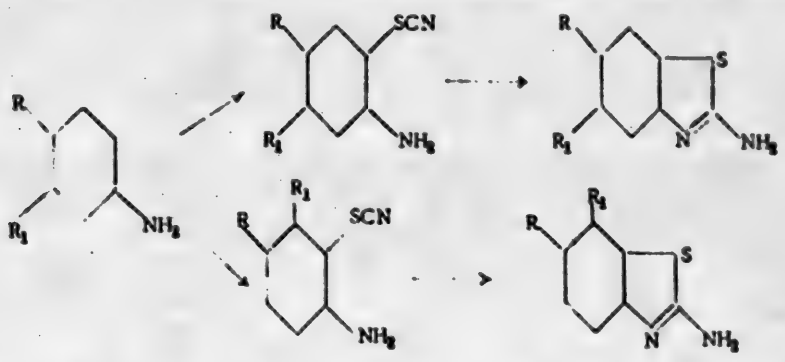
BENZOTHIAZOLE DERIVATIVES

IV. SYNTHESIS OF DERIVATIVES OF 2-AMINOBENZOTHIAZOLE-5,6- AND -6,7-DICARBOXYLIC ACIDS

I. A. Solovyeva and G. I. Arbuzov*

In the thiocyanation of amines of the benzene series containing various substituents in the para-position, the thiocyanogen group easily enters the para-position to the amino group. In the majority of cases the so-formed o-aminothiocyanobenzenes have poor stability and readily isomerize to derivatives of 2-aminobenzothiazole. This process goes especially rapidly in an acid medium at elevated temperature [1,2,3,4].

It was a matter of interest to study the processes of thiocyanation and ring-closure of the obtained o-thiocyanoamino compounds into derivatives of 2-aminobenzothiazoles in the case of 3,4-disubstituted anilines.



In this case formation could be expected of two isomeric thiocyano derivatives which would then give the corresponding two 2-aminobenzothiazoles.

We studied this reaction with reference to the dimethyl ester of 4-aminophthalic acid (R, R_1 = $COOCH_3$), thiocyanation being effected by adding bromine to the acetic acid solution of the amine in presence of 2.4 moles of potassium thiocyanate at −3 to −4° [1].

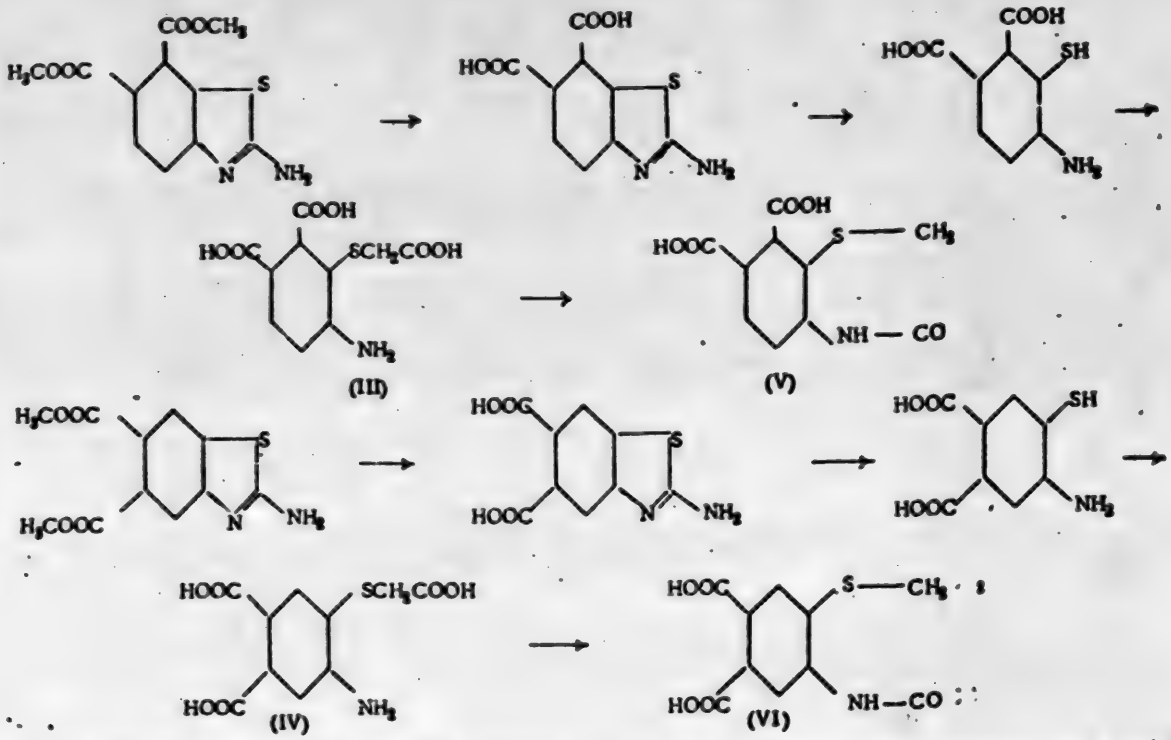
In this way we obtained two isomeric dicarbomethoxy-2-aminobenzothiazoles with melting points of 233-234° and 180-181° (in yields of 78 and 21.5% of the theoretical, respectively). Separation of the isomers was readily effected by taking advantage of the considerably lower solubility in ethyl alcohol of the dicarbomethoxy-2-aminobenzothiazole with m.p. 233-234°.

Consequently in the thiocyanation of the dimethyl ester of 4-aminophthalic acid, the SCN group enters at both of the ortho positions to the amino group.

Saponification of the isomeric dicarbomethoxy-2-aminobenzothiazoles (I and II) readily gave the free 2-aminobenzothiazole dicarboxylic acids. These compounds do not have a definite melting point and are very sparingly soluble in organic solvents (slightly more soluble in pyridine).

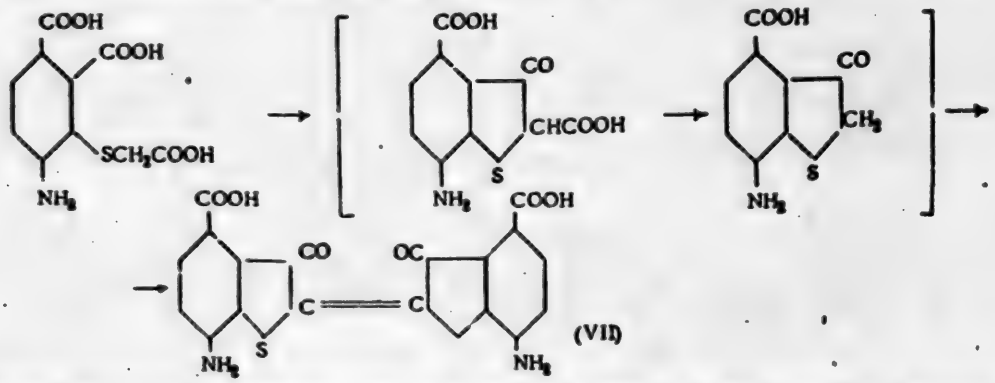
For the determination of their structure, the compounds were heated with concentrated KOH solution at 110-150° until ammonia ceased to come off, and the resultant aminomercaptophthalic acids were converted, by reaction with a salt of chloroacetic acid, into the corresponding 2-aminodicarboxyphenylmercaptoacetic acids which we isolated in the form of the acid potassium salts. In an acid medium, like other similar compounds [5,6,7], these salts are extremely unstable and readily lose water to give the corresponding lactams [derivatives of 3-hydroxy-1,4-benzothiazine (V), (VI)].

* Deceased.



When heated with acetic annydride or caustic alkalies [8,9], the o-carboxyarylmercaptoacetic acids readily undergo intramolecular condensation with formation of derivatives of 3-hydroxythionaphthene, which are converted by oxidation into thioindigoid dyes [7,9].

Out of the 2-aminodicarboxyphenylmercaptoacetic acids prepared by us, only the 5,6-dicarboxy derivative (III) could form a 3-hydroxythionaphthene derivative by this reaction, and therefrom the thioindigoid dye (VII):



The prepared aminodicarboxyphenylmercaptoacetic acids were heated with acetic anhydride in presence of sodium acetate; the reaction mixture was made alkaline and to the filtered solution was added a solution of potassium ferricyanide.

In the case of the substituted mercaptoacetic acid synthesized from the dimethyl ester of 2-aminobenzothiazole dicarboxylic acid with m.p. 180-181°, heating with acetic anhydride resulted in evolution of carbon dioxide, while during oxidation of the obtained solution the color changed from yellow-brown to deep blue-red. Acidification of this solution brought down a precipitate of a dye whose composition corresponded to 4,4'-dicarboxy-7,7'-diaminothioindigo.

When the isomeric 2-aminodicarboxyphenylmercaptoacetic acid, prepared from the dimethyl ester with m.p. 233-234°, was treated similarly, no carbon dioxide came off; nor was formation of a dye observed when potassium ferricyanide was added to the alkaline solution of the reaction product.

In the light of these data we may claim to have established that 2-aminodicarbomethoxybenzothiazole with m.p. 180-181° is the 6,7-dicarbomethoxy derivative (I). Accordingly the product melting at 233-234° will have structure (II).

EXPERIMENTAL

(in collaboration with A. G. Guseva)

Dimethyl Esters of 2-Aminobenzothiazole-5,6dicarboxylic acid and of 2-aminobenzothiazole-6,7dicarboxylic acid

A mixture of 10.45 g dimethyl ester of 4-aminopthalic acid (0.05 mole) and 12 g potassium thiocyanate (0.12 mole) was dissolved in 75 ml 95% acetic acid, and into the resultant solution was stirred at −3 to −4° a solution of 10 g bromine (0.06 mole) in 15 ml 95% acetic acid over a period of 20 minutes. The reaction mass was stirred for 2 hours and left overnight. The liquid was then diluted with 200 ml water, filtered from the small precipitate and neutralized with aqueous ammonia. The light-yellow precipitate was filtered, washed with water and dried. Weight 9.95 g (75% of the theoretical). M.p. 180-210°. The precipitate was crystallized from 200 ml ethyl alcohol. Yield 5.0 g (38% of the theoretical). M.p. 228-230°.

For the purpose of analysis the product was twice recrystallized from ethyl alcohol. Colorless needles, readily soluble in acetone, ethyl alcohol (boiling) and acetic acid; sparingly soluble in cold ethyl alcohol, very sparingly soluble in benzene and ether. M.p. 233-234°.

Found %: N 10.59. $C_{11}H_{10}O_4N_2S$. Calculated %: N 10.53.

The alcoholic filtrate was evaporated to a volume of 10 ml and the precipitate was filtered and dried. Weight 2.85 g (21.5% of the theoretical). M.p. 170-172°.

For the purpose of analysis the compound was twice recrystallized from ethyl alcohol. Yellowish plates. Readily soluble in ethyl and methyl alcohol, acetone and hot acetic acid; almost insoluble in ether and benzene. M.p. 180-181°.

Found %: N 10.41. $C_{11}H_{10}O_4N_2S$. Calculated %: N 10.53.

2-Aminobenzothiazole-5,6-dicarboxylic acid

2.66 g dimethyl ester of 2-aminobenzothiazole-5,6-dicarboxylic acid with m.p. 233-234° (0.01 mole) and a solution of 3.4 g KOH (0.06 mole) in 170 ml water were refluxed for 2½ hours. The alkaline solution was filtered and acidified with hydrochloric acid until the reaction to Congo was sharply acid. After 30 minutes the colorless precipitate was filtered off, mixed with 100 ml hot water, again filtered, washed on the filter with hot water and dried. Yield 2.14 g (90% of the theoretical). Colorless crystalline powder. Almost insoluble in common organic solvents, fairly readily soluble in pyridine, readily soluble in sodium carbonate solution. M.p. above 300°.

For the purpose of analysis the compound was purified by boiling with alcohol and by two reprecipitations from sodium carbonate solution.

Found %: N 11.88, equivalent 120.20. $C_9H_6O_4N_2S$. Calculated %: N 11.76; equivalent 119.07.

2-Aminobenzothiazole-6,7-dicarboxylic acid

To 2.66 g dimethyl ester of 2-aminobenzothiazole-6,7-dicarboxylic acid with m.p. 180-181° (0.01 mole) was added a solution of 3.13 g KOH (0.056 mole) in 150 ml water, and the mixture refluxed for 1½ hours. The alkaline solution was filtered from the small precipitate and acidified with hydrochloric acid until the reaction to Congo was sharply acid. After 30 minutes the colorless precipitate was filtered, stirred with 100 ml hot water, again filtered, washed with hot water on the filter and dried. Yield 2.19 g (92% of the theoretical).

Colorless crystalline powder. Almost insoluble in the usual solverts, rather more soluble in pyridine, readily soluble in sodium carbonate solution. M.p. above 300°.

For the purpose of analysis the substance was purified by digestion with alcohol and by two reprecipitations from sodium carbonate solutions.

Found %: N 11.53; equivalent 119.70. $C_9H_6O_4N_2S$. Calculated %: N 11.76; equivalent 119.07.

Lactam of 2-amino-5,6-dicarboxyphenylmercaptoacetic acid

1.33 g dimethyl ester of 2-aminobenzothiazole-6,7-dicarboxylic acid with m.p. 180-181° was mixed with a solution of 2.8 g KOH in 2.5 ml water, and the mixture refluxed for 3 hours on an oil bath with gradual rise of temperature from 110° to 130° (oil temperature); after that, heating was continued in the open flask at 150-155° until ammonia ceased to come off (30-40 minutes). To the cooled mixture was added a solution of 0.47 g chloroacetic acid and 0.28 g KOH in 3 ml water, and the mixture heated for 30 minutes on the water bath at 65-75°. To the cooled solution was added 6.5 ml glacial acetic acid and the resultant syrupy mass was diluted with 50 ml alcohol. The alcohol was decanted off, the precipitate of the acid potassium salt of 2-amino-5,6-dicarboxyphenylmercaptoacetic acid was washed with absolute alcohol until completely crystallized, rapidly filtered, and dried in a vacuum desiccator. Weight 1.1 g. The product was very hygroscopic and without further purification was used for the preparation of the thioindigoid dye.

When the alkaline solution of 2-amino-5,6-dicarboxyphenylmercaptoacetic acid was acidified with hydrochloric acid, the acid solution deposited on standing a precipitate of the lactam; this was filtered, washed with water and recrystallized from hot water. Fine yellow needles, soluble in hot water, insoluble in alcohol, ether, benzene and acetic acid. Sinters at above 300°.

Found %: N 5.36; equivalent 125.8 $C_{10}H_{17}O_5NS$ Calculated %: N 5.53; equivalent 126.6.

4,4'-Dicarboxy-7,7'-diaminothioindigo

To 1.1 g of the acid potassium salt of 2-amino-5,6-dicarboxyphenylmercaptoacetic acid was added 3.2 ml acetic anhydride and 0.66 g calcined sodium acetate, and the mixture was boiled for 45 minutes. Carbon dioxide came off during the treatment. To the cooled reaction mass was then added 12 ml 20% NaOH solution; the solution was boiled for 20 minutes, cooled and filtered. To the yellow-brown filtrate was added a solution of 5.26 g potassium ferricyanide in 20 ml water, the color of the solution changing to blue-red. The mixture was shaken for a few minutes and acidified with hydrochloric acid until acid to Congo. The red-brown precipitate of the dye was filtered, washed with water and alcohol and dried

For the purpose of purification the dye was reprecipitated from sodium carbonate solution with hydrochloric acid, filtered, washed, dried and recrystallized from ethyl alcohol. Light-brown crystals, m.p. 210-212°. Fairly good solubility in methyl and ethyl alcohol and acetic acid; less good in acetone. Insoluble in ether and benzene; readily soluble in sodium carbonate solution.

Found %: N 6.98. $C_{18}H_{16}O_4N_2S_2$. Calculated %: N 6.76.

Lactam of 2-amino-4,5-dicarboxyphenylmercaptoacetic acid

To 1.33 g dimethyl ester of 2-aminobenzothiazole-5,6-dicarboxylic acid with m.p. 233-234° was added a solution of 2.8 g KOH in 2.5 ml water the mixture was refluxed in a flask on an oil bath at 120-130° (oil temperature) for 4 hours and then heated in the open flask at 140-150° until ammonia ceased to come off (45-60 minutes). To the cooled mixture was added a solution of 0.47 g chloroacetic acid and 0.28 g KOH in 3 ml water, and the mixture was heated for 30 minutes on the water bath at 65-70°. To the cooled solution was added dropwise 2.5-3 ml glacial acetic acid when a precipitate was formed, and the viscous mass was carefully stirred with 50 ml alcohol. The precipitate of the acid potassium salt of 2-amino-4,5-dicarboxyphenylmercaptoacetic acid was filtered off, washed a few times with alcohol and dried at 80°. Weight 1.22 g. Readily soluble in water, very sparingly in ethyl alcohol.

When the 2-aminocarboxyphenylmercaptoacetic acid was heated with acetic anhydride in presence of sodium acetate, no carbon dioxide was evolved. When the reaction mass was made alkaline and treated with potassium ferricyanide, formation of a dye was not observed. On acidification with hydrochloric acid of the alkaline solution of 2-aminodicarboxyphenylmercaptoacetic acid, gradual separation (quicker if heated) occurred of a colorless precipitate of the lactam of 2-amino-4,5-dicarboxyphenylmercaptoacetic acid. This was filtered off, washed with water and recrystallized from hot water. Fine colorless crystals Readily soluble in hot water, insoluble in alcohol, benzene, ether and acetic acid Sinters at a temperature above 300°.

Found %: N 5.32, equivalent 127.2. $C_{10}H_{17}O_5NS$ Calculated %: N 5.53, equivalent 126.6.

SUMMARY

1. The thiocyanation of the dimethyl ester of 4-aminophthalic acid was studied in a medium of acetic acid. It was shown that a mixture is formed of the esters of 2-aminobenzothiazole-5,6- and -6,7-dicarboxylic acids.

2. The lactams of 4,5- and 5,6-dicarboxy-2-aminophenylmercaptoacetic acids were prepared.

3. 4,4'-Dicarboxy-7,7'-diaminothioindigo was synthesized from the ester of 2-aminobenzothiazole-6,7-dicarboxylic acid.

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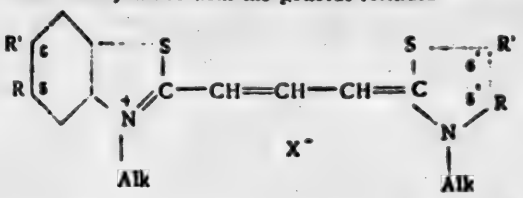
Received July 2, 1952

All-Union Cinephoto Research Institute

COPLANARITY OF THE DIMETHYLAMINO GROUP WITH THE BENZENE RING AND ITS AUXOCHROMIC ACTION. I

A. I. Kiprianov and I. N. Zhmurova

The influence of the dimethylamino group on the color of a dye is associated with transfer of the free electron pair of the nitrogen atom to the benzene ring and subsequently to a conjugated chain [1]. A necessary condition for such an electron transfer is the location of the dimethylamino group in the same plane as the benzene ring. If a voluminous substituent is introduced into the ortho-position to the dimethylamino group, the latter moves out of the plane of the ring and its influence on the color is partly or completely eliminated. The weakening of the auxochromic action of the dimethylamino group due to introduction of a substituent in the ortho-position has been described by I. I. Levkoev with reference to cyanine dyes [2] and by Remington with reference to dialkylanilines [3]. The observations of I. I. Levkoev related mainly to substituents of a polar character for which it is difficult to segregate the steric effect from the electronic effects. We have investigated this phenomenon in cyanine dyes containing bulky alkyl radicals in the ortho-position to the amino groups. To a first approximation the electronic effect of such radicals may be neglected. With this objective we synthesized a series of new tetrasubstituted thiacarbocyanines with the general formula:



where R = NH_2, $NHCOCH_3$ or $N(CH_3)_2$, R' = CH_3 or $C(CH_3)_3$, Alk = CH_3 or C_2H_5, X = anion of the dye.

The absorption maxima and the molecular extinctions of these dyes are enumerated in Table 1. For comparison the table includes data for some previously known dyes (1,2,4,7,10).

TABLE 1

No.	R	R'	Alk	λ_{max} in mμ	$\epsilon_{max} \cdot 10^{-4}$
1	H	H	CH_3	558	16.5
2	H	CH_3	C_2H_5	563	14.5
3	H	$C(CH_3)_3$	CH_3	563	14.9
4	$NHCOCH_3$	H	C_2H_5	577	–
5	$NHCOCH_3$	CH_3	C_2H_5	575	–
6	$NHCOCH_3$	$C(CH_3)_3$	CH_3	568	–
7	NH_2	H	C_2H_5	596	–
8	NH_2	CH_3	C_2H_5	594	–
9	NH_2	$C(CH_3)_3$	CH_3	592	–
10	$N(CH_3)_2$	H	C_2H_5	608	8.2
11	$N(CH_3)_2$	CH_3	C_2H_5	575	10.1
12	$N(CH_3)_2$	$C(CH_3)_3$	CH_3	570	14.1

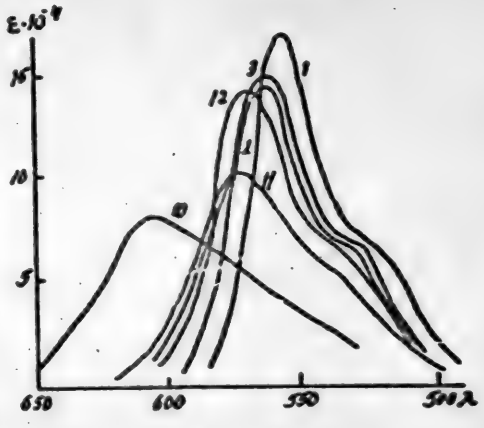


Fig. 1.

The absorption curves of preparations 1,2,3,10,11 and 12 are shown in Fig. 1.

In themselves the alkyl groups R' exhibit little influence on the absorption (preparations 1,2,3). Substitution of the hydrogen atoms in the 5,5'-position by dimethylamino groups sharply shifts the absorption curve. The absorption maximum is displaced into the long-wave part of the spectrum to the extent of 50 mμ, the absorption band is broadened, and its intensity lowered (10). The red-violet color of the alcoholic solution of the dye changes to dark-blue. If, however, methyl radicals are introduced in the 6,6'-position, i.e. in the ortho-position to the dimethylamino groups, then the influence of the dimethylamino groups is partly paralyzed as it were. The

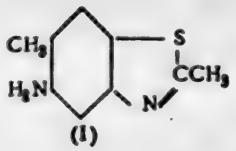
absorption maximum of the corresponding preparation (11) differs from that of the unsubstituted thiacarbocyanine by only 12 mμ, the absorption intensity increases, and in alcoholic solution the dye acquires a violet color. Replacement of the two methyl groups by two tertiary butyl groups causes the absorption curve to approach still more closely the curve of the unsubstituted thiacarbocyanine. In this case the difference in the positions of the absorption maxima is 7 mμ, and if we compare such a tetrasubstituted dye (12) with the disubstituted dye containing the same tertiary butyl groups but not containing dimethylamino groups (3), then we find that their absorption curves are almost identical. It is impossible to distinguish between these two dyes by the color of their alcoholic solutions. Alkyl radicals in ortho-positions are substantially without influence on the auxochromic action of acetylamino and unsubstituted amino groups (preparations 4,5,6 and 7,8,9). A brief exposition of this part of our investigation has already been published [4].

Compounds that we prepared later are listed in Table 2 and represent isomers of the dyes in Table 1; they differ from the latter in the distribution of the alkyl and amino groups. As we see from Table 2 and Fig. 2, in these preparations also the alkyl group adjacent to the dimethylamino group partly suppresses the auxochromic effect of the latter. In this table are also listed the known dyes 13, 15, 18 and 21 for comparison.

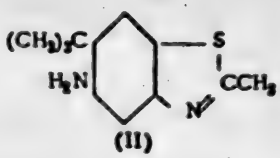
Preparation of the above-described tetrasubstituted thiacarbocyanines necessitated as intermediates the benzothiazole derivatives (I) and (II) as well as their isomers (III) and (IV).

TABLE 2

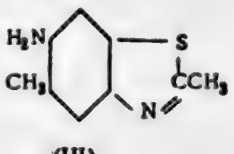
No.	R	R'	Alk	λ_{max} in mμ	$\epsilon_{max} \cdot 10^{-4}$
1	H	H	CH_3	558	16.5
13	CH_3	H	C_2H_5	563	14.5
14	$C(CH_3)_3$	H	CH_3	565	14.4
15	H	$NHCOCH_3$	C_2H_5	579	–
16	CH_3	$NHCOCH_3$	CH_3	575	–
17	$C(CH_3)_3$	$NHCOCH_3$	CH_3	570	–
18	H	NH_2	C_2H_5	596	–
19	CH_3	NH_2	CH_3	594	–
20	$C(CH_3)_3$	NH_2	CH_3	592	–
21	H	$N(CH_3)_2$	C_2H_5	612	11.7
22	CH_3	$N(CH_3)_2$	CH_3	575	12.4
23	$C(CH_3)_3$	$N(CH_3)_2$	CH_3	570	14.3



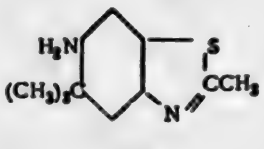
(I)



(II)

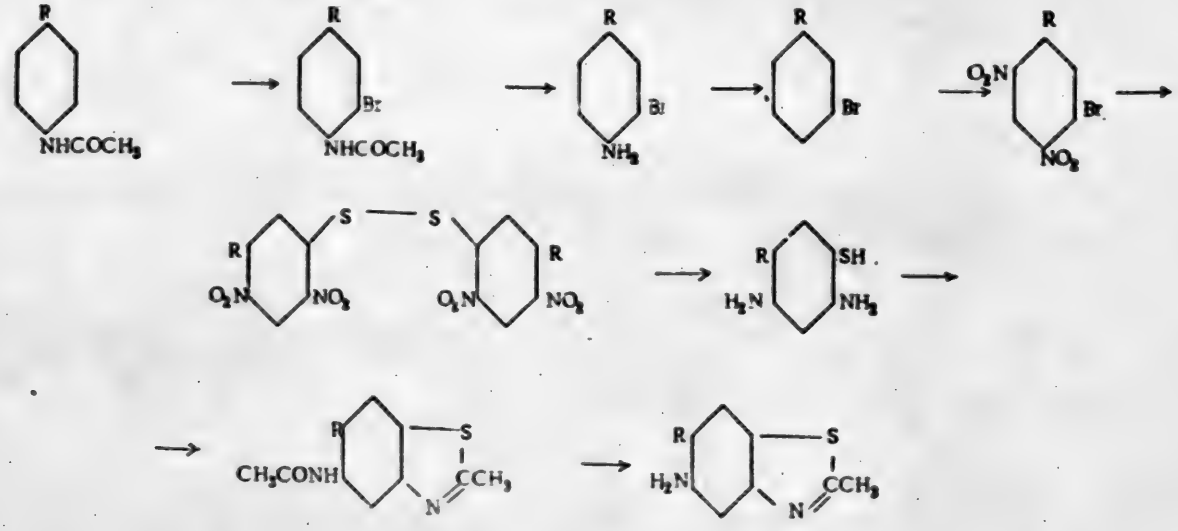


(III)

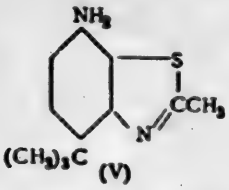


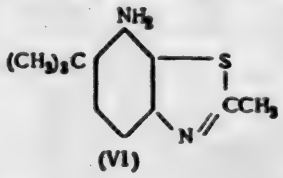
(IV)

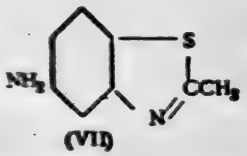
Of these four bases, only 2,6-dimethyl-5-aminobenzothiazole (I) and its isomer (III) have been described in patents [5,9]; the other two were unknown. We prepared (I) and (II) by the following scheme [R = CH_3, $C(CH_3)_3$]:



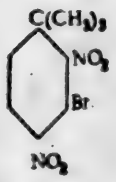
There can be no doubt about the structure of preparation (I) since 3-bromo-4,6-dinitrotoluene, the intermediate in its synthesis, has been described in the literature [6]. Concerning base (II), it was necessary to demonstrate that the structure was that stated and not that of one of its isomers (V, VI, VII):

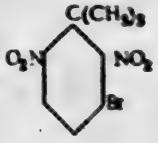

(V)


(VI)


(VII)

which could be obtained if dinitro products with the structures (VIII) and (IX) were formed in the nitration of m-bromo-tert. butylbenzene:


(VIII)


(IX)

The following facts support the assumption that we actually obtained base (II).

1. Formation of nitro products (VIII) and (IX) during nitration of m-bromo-tert. butylbenzene is highly improbable due to steric hindrance.

2. When the quaternary salts of benzothiazole (V) and (VI) are condensed with ethyl orthoformate, they must give thiacarbocyanines whose color differs but slightly from that of the thiacarbocyanine not containing amino groups. E. P. Sych showed that in 7,7'-positions, amino groups have little influence on the color of thiacarbocyanines [7]. Moreover, our base gave a deeply colored thiacarbocyanine with an absorption maximum at 592 mμ.

3. Structures (V) and (VII) must be excluded because deamination of our base yielded 2-methyl-6-tert. butylbenzothiazole. This was proved by the absence of depression in melting point determinations of mixed specimens of picrates of our base and of 2-methyl-6-tert. butylbenzothiazole.

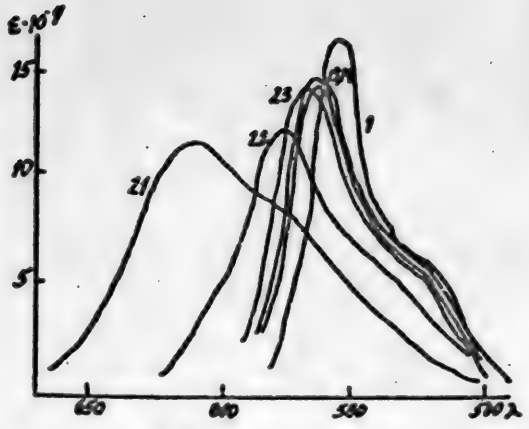
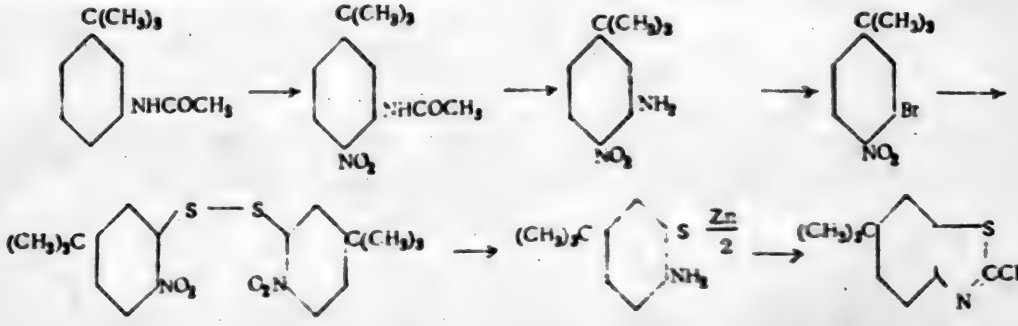


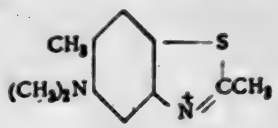
Fig. 2.

We synthesized 2-methyl-6-tert. butylbenzothiazole by the following scheme:

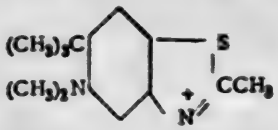


The dye 3 was prepared from the quaternary salt of 2-methyl-6-tert. butylbenzothiazole.

The acetyl derivatives of bases (I) and (II) were likewise converted into the quaternary salts and then into dyes 5 and 6. Saponification of the acetyl groups of the dyes gave dyes 8 and 9. Treatment of bases (I) and (II) with excess of dimethyl sulfate gave us the quaternary salts (X) and (XI) from which dyes 11 and 12 were prepared.

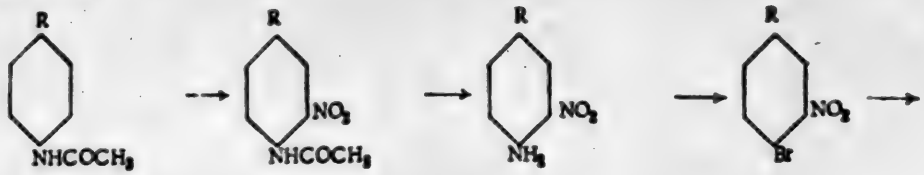


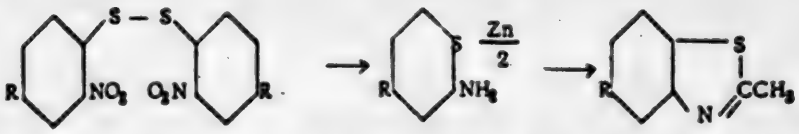
(X)



(XI)

The isomeric bases (III) and (IV) were prepared through 2-methyl-5-alkylbenzothiazoles by the following route [R = CH_3 or $C(CH_3)_3$]:

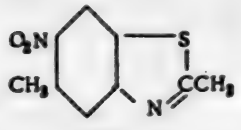




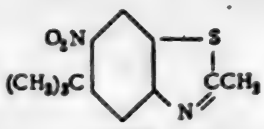
This synthetic scheme was worked out by A. I. Kiprianov and E. D. Sych for 2,5-dimethylbenzothiazole [8]. We prepared 2-methyl-5-tert. butylbenzothiazole for the first time. We synthesized dye 14 from its quaternary salt.

2-Methyl-5-alkylbenzothiazoles were nitrated. Nitration of 2,5-dimethylbenzothiazole gives two isomeric nitro products, one of which melts at 152-154° and the other at 133-134°. Reduction of the product with m.p. 152-154° with tin chloride and hydrochloric acid gave an amine with m.p. 168°. According to one patent [9], this is the m.p. of 2,5-dimethyl-6-aminobenzothiazole. For this reason we assigned the structure (XII) to the nitro product with m.p. 152-154°.

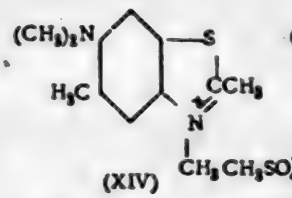
The second isomer with m.p. 133-134° is evidently 2,5-dimethyl-4-nitrobenzo thiazole. It was not further investigated.



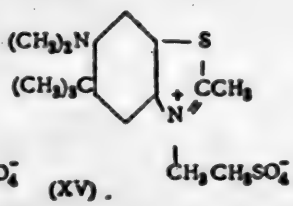
(XII)



(XIII)



(XIV)



(XV)

Nitration of 2-methyl-5-tert. butylbenzothiazole gave only one nitro product: 2-methyl-5-tert. butyl-6-nitrobenzothiazole (XIII).

Its structure was confirmed by the deep color of dye 20. Acetylation of preparations (III) and (IV) gave the corresponding acetyl derivatives; from the quaternary salts of the latter, dyes 16 and 17 were obtained. Saponification of the acetyl groups in these dyes led to dyes 19 and 20. Action of an excess of dimethyl sulfate on bases (III) and (IV) gave us the quaternary salts (XIV) and (XV), from which the dyes 21 and 22 were obtained.

Apart from 3 and 14, all the dyes that we synthesized in the first and second series are amorphous powders which could only be purified by chromatography. Their yields did not exceed 23%. Owing to the difficulty of purification, dyes 8, 9, 16, 19 and 20 were not isolated in the pure state.

EXPERIMENTAL

2,6-Dimethyl-5-acetylaminobenzothiazole and 2,6-dimethyl-5-aminobenzothiazole (I). To a warm solution of 26 g 3-bromo-4,6-dinitrotoluene (prepared by nitration of m-bromotoluene [9]) in 250 ml alcohol was gradually added with shaking a hot mixture of 18 g crystalline sodium sulfide, 2.4 g sulfur and 10 ml alcohol. After all had been added, the mixture was boiled for 3 hours. The yellow precipitate of 2,2',4,4'-tetranitro-5,5'-dimethyldiphenyldiphenyldisulfide was filtered and washed with water. Yield 18 g (82%)*. 13 g disulfide, 30 g tin and 150 ml concentrated HCl were gently refluxed until all the tin had dissolved and then boiling was continued for an hour. The whole of the disulfide dissolved. The solution was diluted with water and the tin was precipitated by heating with hydrogen sulfide. The precipitate was filtered, the solution was evaporated to dryness in vacuum. To the dry residue was added 30 ml acetic anhydride and 100 ml glacial acetic acid. The mixture was boiled for 3 hours, then diluted with water and neutralized with ammonia. The residue (2,6-dimethyl-5-acetylaminobenzothiazole and residual tin) was dried and extracted with benzene in a Soxhlet apparatus. Yield 7 g (31%). Recrystallization from benzene gave fine, slightly yellow needles, m.p. 175-178°**, according to patent data [5] the m.p. is 178°.

Methiodide: light-yellow prisms (from alcohol), m.p. 216-218° with decomposition.

Found %: I 35.16, 35.18. $C_{13}H_{15}ON_2SI$. Calculated %: I 35.08.

Precipitation of tin by hydrogen sulfide after reduction of the disulfide is not obligatory. The solution may be evaporated to dryness on the water bath after completion of the reduction, and the dry residue (a mixture of tin salts and the hydrochloride of 2,4-diamino-5-methylthiophenol) may be worked up as described above. By this method the yield is not reduced.

2,5-Dimethyl-6-aminobenzothiazole was prepared by heating 1.5 g of the preceding product with 10 ml dilute sulfuric acid for 30 minutes. The solution was digested with carbon, filtered and neutralized with ammonia. Yield 0.9 g (75%). Colorless needles (from water), m.p. 141-143° (According to patent data [5], 143°).

Heating of 0.2 g of the base with 0.4 g dimethyl sulfate at 100-110° for 4 hours gave the methiodide of 2,5-dimethyl-6-dimethylaminobenzothiazole. Yellow needles (from alcohol), m.p. 246-247° with decomposition.

Found %: I 36.84, 36.73. $C_{13}H_{17}N_2SI$. Calculated %: I 36.49.

m-Bromo-tert. butylbenzene was prepared, by analogy with m-bromotoluene [10], by bromination of p-acetamino-tert. butylbenzene [11] followed by saponification and deamination. m-Bromo-tert. butylbenzene was obtained in the form of a yellow oil with b.p. 237-239°, in agreement with the literature data [12]. Yield 36% calculated on p-acetamino-tert. butylbenzene.

3-Bromo-4,6-dinitro-tert. butylbenzene. 21.7 g 3-bromo-tert. butylbenzene was gradually added with stirring at the usual temperature to a mixture of 13 ml nitric acid (sp.gr. 1.5) and 30 ml concentrated sulfuric acid. The mixture was then stirred for 2 hours at 110-120° and poured into water. The solidified nitro product was filtered and recrystallized from alcohol. Cream-colored tablets with m.p. 92-94°. Yield 12.3 g (30.8%).

Found %: N 9.21, 9.07. $C_{10}H_{11}O_4N_2Br$. Calculated %: N 9.21.

2-Methyl-5-acetylamino-6-tert. butylbenzothiazole and 2-methyl-5-amino-6-tert. butylbenzothiazole (II) were prepared similarly from the methyl analogs. From 11 g 3-bromo-4,6-dinitro-tert. butylbenzene, by treatment with alcoholic Na_2S_2, was obtained 6.4 g (69%) of 2,2',4,4'-tetranitro-5,5'-ditert. butyldiphenyldisulfide. The disulfide was reduced with 27 g tin and 55 ml concentrated HCl. Boiling was continued for 3½ hours after the tin had dissolved. The tin was precipitated with hydrogen sulfide, the filtrate was evaporated, and the dry residue boiled for an hour with 30 ml acetic anhydride. The excess of acetic anhydride was decomposed with water, and the solution was neutralized with ammonia; the filtered and dried precipitate was extracted with benzene. After recrystallization from benzene, 2-methyl-5-acetylamino-6-tert. butylbenzothiazole was obtained in the form of a yellowish, amorphous powder which gradually softened, without melting, at 150-170°, yield 1.8 g (27%).

Found %: N 10.54, 10.65. $C_{14}H_{18}ON_2S$. Calculated %: N 10.68.

* All yields are stated in percentages of the theoretical.

** All the melting points and boiling points in this paper have been corrected.

TABLE 3

No.	Name of dye	Base	Alkylating agent	Ethyl ortho-formate	Yield in % of theory	Gross formula	Nitrogen analysis, %	
							found	calc.
5	Bis-[3-ethyl-5-acetylamino-6-methylbenzothiazole (2)]-trimethinecyanine-p-toluenesulfonate	2,6-Dimethyl-5-acetylaminobenzothiazole 0.2 g	Ethyl p-toluenesulfonate 0.14 g	0.4	14.5	$C_{34}H_{38}O_5N_6S_3$	8.15, 8.28	8.26
6	Bis-[3-methyl-5-acetylamino-6-tert. butylbenzothiazole (2)]-trimethinecyanine-p-toluenesulfonate	2-Methyl-5-acetylamino-6-tert.butylbenzothiazole 0.1 g	Methyl p-toluenesulfonate 0.07 g	0.2	12	$C_{38}H_{46}O_5N_6S_3$	7.60, 7.41	7.63
16	Bis-[3,5-dimethyl-6-acetylaminobenzothiazole (2)]-trimethinecyanine-p-toluenesulfonate	2,5-Dimethyl-6-acetylaminobenzothiazole 0.2 g	Methyl p-toluene sulfonate 0.14 g	0.4	30.9 (unpurified)	$C_{32}H_{34}O_5N_6S_3$	Not isolated in pure state due to poor solubility	
17	Bis-[3-methyl-5-tert.butyl-6-acetylaminobenzothiazole (2)]-trimethinecyanine-p-toluenesulfonate	2-Methyl-5-tert.butyl-6-acetylaminobenzothiazole 0.1 g	Methyl p-toluene sulfonate 0.07 g	0.2	20.7	$C_{38}H_{46}O_5N_6S_3$	7.80, 7.77	7.63
11	Bis-[3,6-dimethylaminobenzothiazole (2)]-trimethinecyanine methosulfate	2,6-Dimethyl-5-aminobenzothiazole 0.2 g	Dimethyl sulfate 0.4 g	0.4	7.9	$C_{26}H_{34}O_4N_6S_3$	9.67, 9.73	9.96
12	Bis-[3-methyl-5-dimethylamino-6-tert.butylbenzothiazole (2)]-trimethinecyanine methosulfate	2-Methyl-5-amino-6-tert. butylbenzothiazole 0.1 g	Dimethyl sulfate 0.2 g	0.2	7	$C_{32}H_{46}O_4N_6S_3$	9.00, 8.85	8.81
22	Bis-[3,5-dimethyl-6-dimethylaminobenzothiazole (2)]-trimethinecyanine methosulfate	2,5-Dimethyl-6-aminobenzothiazole 0.2 g	Dimethyl sulfate 0.4 g	0.4	7.9	$C_{28}H_{34}O_4N_6S_3 \cdot 3H_2O$	9.10, 9.23	9.15
							Presence of water of crystallization demonstrated	
23	Bis-[3-methyl-5-tert. butyl-6-dimethylaminobenzothiazole (2)]-trimethinecyanine methosulfate	2-Methyl-5-tert. butyl-6-aminobenzothiazole 0.2 g	Dimethyl sulfate 0.4 g	0.4	22.7	$C_{32}H_{46}O_4N_6S_3$	8.59, 8.54	8.81

1.5 g of the preceding compound was digested for 30 minutes with 30 ml dilute sulfuric acid. Neutralization with ammonia led to separation of 2-methyl-5-amino-6-tert. butylbenzothiazole. The product could only be recrystallized after purification by running the benzene solution through a column containing alumina. Colorless needles (from water), m.p. 126-127°. Yield 0.6 g (46%).

Found %: N 12.01, 12.03. $C_{11}H_{14}N_2S \cdot H_2O$. Calculated %: N 11.76.

Water of crystallization was found to be present.

2-Methyl-6-tert. butylbenzothiazole. p-Acetamino-tert. butylbenzene was nitrated [13], the acetamino group was saponified and the m-amino tert. butylbenzene was subjected to deamination, reduction of the nitro group and acetylation. The m-acetamino-tert. butylbenzene was again nitrated [13] and the acetyl group was saponified. 14.2 g of so-prepared 3-amino-4-nitro-tert. butylbenzene was dissolved in a mixture of 40 ml concentrated sulfuric acid and 60 ml water. The solution was diazotized and added dropwise to a boiling solution of Cu_2Br_2 while steam was passed through. 3-Bromo-4-nitro-tert.butylbenzene was distilled off in the form of an oil which was extracted with benzene and vacuum-distilled, b.p. 142-144°. Yield 10.2 g (54%). The preparation is not described in the literature.

10.2 g 3-bromo-4-nitro-tert. butylbenzene was dissolved in 25 ml alcohol and treated with a hot mixture of 6.1 g crystalline sodium sulfide, 0.9 g sulfur and 10 ml alcohol. After 2 hours' heating on the water bath, 2,2'-dinitro-4,4'-ditert.butyldiphenyldisulfide came down in the form of a viscous, yellow mass. The disulfide was separated from the liquid by decantation, washed with water and alcohol and dissolved by heating in 50 ml acetic acid. Into the cooled solution was gradually stirred 15 g zinc dust and 30 ml concentrated HCl. Stirring was continued for another hour and the solution was then filtered, diluted with water and saturated with sodium acetate. The white precipitate of the zinc mercaptide was filtered and dried, after which its weight was 3.5 g. It was boiled for an hour with 20 ml acetic anhydride. The excess of acetic anhydride was decomposed with water and the solution was made alkaline. The separated oil was extracted with benzene and vacuum-distilled. B.p. 134-136° at 15 mm. Yield 1.5 g or 44% calculated on the mercaptide.

Picrate: yellow powder, m.p. 137-139°.

Found %: N 12.96, 13.10. $C_{11}H_{15}NS \cdot C_6H_3O_7N_3$. Calculated %: N 12.90.

Methyl perchlorate: colorless needles (from alcohol), m.p. 210-211° with decomp.

Found %: Cl 10.85, 11.05. $C_{13}H_{18}O_4NSCl$. Calculated %: Cl 11.04.

The same preparation was obtained in the form of picrate by deamination of 2-methyl-5-amino-6-tert. butylbenzothiazole for the purpose of confirming the structure of the latter. 0.3 g amino compound was dissolved in 10 ml alcohol and 5 ml concentrated sulfuric acid was added. The mixture was cooled to 0° and diazotized with a solution of 0.2 g sodium nitrite in 2 ml water. The mixture was then heated on the water bath for 30 minutes, diluted with water, neutralized with sodium carbonate and extracted with ether. The oil remaining after distillation of the ether was dissolved in alcohol and mixed with an alcoholic solution of picric acid. After several recrystallizations from alcohol, a picrate with m.p. 137-139° was obtained. Yield 0.05 g. No m.p. depression of the mixture with the picrate of 2-methyl-6-tert. butylbenzothiazole prepared by the above-described method.

2-Methyl-5-tert.butylbenzothiazole was obtained in a similar manner to the above base. 22.5 g 3-nitro-4-amino-tert.butylbenzene [13] gave 14 g (47%) 3-nitro-4-bromo-tert.butylbenzene. A yellow oil, b.p. 174-175° (30 mm). According to the literature [14] 3-nitro-4-bromo-tert.butylbenzene boils at 124-126° (3 mm).

Treatment of 14 g of the nitrobromo derivative with alcoholic Na_2S_2 followed by reduction with zinc dust yielded 7.9 g of the corresponding zinc mercaptide, from which was obtained 3.3 g (49%, calculated on the mercaptide) 2-methyl-5-tert.butylbenzothiazole. Yellow oil, b.p. 153-156° (10 mm).

Picrate: yellow tablets, m.p. 147-149°.

Found %: N 12.78, 12.72. $C_{11}H_{13}NS \cdot C_6H_3O_7N_3$. Calculated %: N 12.90.

Methiodide: colorless needles (from alcohol), m.p. 228° with decomposition.

Found %: I 36.55, 36.79. $C_{12}H_{16}NSI$. Calculated %: I 36.60.

2,5-Dimethyl-6-nitrobenzothiazole (XII) 6 g 2,5-dimethylbenzothiazole [8] was added gradually at 20-25° to a mixture of 4 4 ml nitric acid (sp gr 1 4) and 12 ml concentrated sulfuric acid The mixture was left for 15 minutes at room temperature and poured into water The nitro product, weight 5 5 g (75%), came out in the form of a slightly yellowish precipitate, m p 105 112° Repeated fractional crystallization from alcohol gave 1.9 g 2,5-dimethyl 6 nitrobenzothiazole Cream-colored needles with m p 152-154°.

Found % N 13 48, 13 30. $C_9H_8O_2N_2S$. Calculated %. N 13.46.

A second isomeric nitro product isolated in quantity of 0 9 g, had m p 133-134°. In all probability it is 2,5-dimethyl-4-nitrobenzothiazole

2-Methyl 5-tert butyl 6-nitrobenzothiazole (XIII) 1 5 g 2-methyl-5-tert butylbenzothiazole was gradually added to a mixture of 1 2 ml nitric acid (sp gr 1 4), and 3 ml concentrated sulfuric acid The mixture was then heated and stirred for an hour at 90-100° and poured into water The nitro product was filtered and recrystallized several times from alcohol. Cream-colored needles, m p 122-124° Yield 0 7 g (40%)

Found % N 10.91, 10 81 $C_{12}H_{14}O_2N_2S$ Calculated % N 11 20

2,5-Dimethyl-6-aminobenzothiazole (III) and 2,5-dimethyl-6-acetylaminobenzothiazole. 1 9 g 2,5-dimethyl-6-nitrobenzothiazole was mixed with a solution of 5 6 g stannous chloride in 15 ml concentrated HCl The mixture was heated for 10 minutes at a gentle boil After a few hours the precipitated double salt of the amine with stannous chloride was filtered and treated with excess caustic alkali The amine was crystallized from benzene. Colorless needles, m p 167-168° according to the patent data [9] the m p is 168°. Yield 1.5 g (94%). Treatment of 0.5 g amine with 2 ml acetic anhydride gave 0 5 g 2,5-dimethyl-6-acetylaminobenzothiazole. Colorless needles (from water), m.p. 226-228°.

Found % N 12 41 12 47 $C_{11}H_{12}ON_2S$ Calculated % N 12 75.

Methiodide: colorless prisms (from alcohol), m p 261-262° with decomp

Found % I 35 25 35 13 $C_{12}H_{15}ON_2SI$ Calculated % I 35 08.

2-Methyl-5-tert butyl-6-aminobenzothiazole (V) and 2-methyl 5 tert butyl 6 acetylaminobenzothiazole were similarly prepared Stannous chloride reduction of 0 5 g 2-methyl 5 tert butyl-6-nitrobenzothiazole gave 0 4 g (90%) of the amino compound. Cream colored needles (from ligroin) m.p. 186-188°.

Found % N 12 75 $C_{12}H_{16}N_2S$ Calculated %: N 12 73

From 0 2 g amine was obtained 0 2 g 2-methyl-5-tert butyl-6 acetylaminobenzothiazole. Colorless needles (from a mixture of 1 vol benzene and 5 vols ligroin) m p 193 195°

Found % N 10 49, 10 39 $C_{14}H_{18}ON_2S$. Calculated % N 10 68.

Dyes

Tetrasubstituted thiacarbocyanines

a) Dyes with dimethylamino groups were prepared in the following manner 1 mole of the corresponding amino derivative of 2 methylbenzothiazole and 3 moles dimethyl sulfate were heated for 4 hours at 100-110° Methylation of the amino group then took place at the same time as a quaternary salt was formed at the nitrogen atom of the thiazole ring To the quaternary salt was added a few milliliters of pyridine and the equivalent amount of ethyl orthoformate. The mixture was boiled for 20 minutes, after which the pyridine was distilled off in vacuum; the dye was dissolved in chloroform and chromatographed several times on alumina The dye isolated after the final chromatographic treatment was dissolved in 95% alcohol and filtered for removal of traces of alumina After evaporation of the alcohol, the dye was isolated in the form of a amorphous powder Dyes 11, 12, 22, 23 (Tables 1 and 2) were prepared in this manner.

b) Dyes with acetylamino groups Quaternary salts were prepared by heating equivalent amounts of the corresponding acetylamino derivative of 2-methylbenzothiazole and the methyl (or ethyl) ester of p-toluenesulfonic acid at 130-140° for 1½2 hours Preparation and purification of the dyes were carried out as described above. The dyes 5, 6, 16 and 17 (Tables 1 and 2) were prepared in this manner The yields and analytical data of the dyes are detailed in Table 3 The numbers assigned to the dyes correspond to their numbers in Tables 1 and 2. Yields of purified preparations are given in all cases, except for 16.

c) Dyes with amino groups. These were obtained by saponification of the acetyl groups in the acetylamino-substituted dyes. The unpurified dyes, prepared as described above, were boiled with 20% sulfuric acid for 20-30 minutes, after which the acid was neutralized with ammonia and the dye was filtered, dissolved in alcohol and the chloride of the dye precipitated with aqueous NaCl solution. The saponification could be performed by heating the dye for 20-30 minutes at 100-120° with a mixture of equal amounts of concentrated sulfuric acid and glacial acetic acid. After cooling, the solution was diluted with water and neutralized with ammonia. The following dyes were prepared in this way: bis-[3-ethyl-5-amino-6-methylbenzothiazole(2)] trimethinecyanine chloride — 8 in table; bis-[3-methyl-5-amino-6-tert-butylbenzothiazole (2)] trimethinecyanine chloride — 9; bis-[3,5-dimethyl-6-amino-benzothiazole (2)]-trimethinecyanine chloride —19; bis-[3-methyl-5-tert.butyl-6-aminobenzothiazole (2)]-trimethinecyanine chloride —20.

These four dyes have very poor solubility in alcohol and still worse in chloroform; purification by chromatography is therefore impossible. We were therefore unable to isolate them in the pure state. Only their absorption curves were investigated in alcoholic solutions of undetermined concentration.

Bis-[3-methyl-5-tert.butylbenzothiazole (2)]-trimethinecyanine chloride —3. 0.2 g 2-methyl-5-tert. butyl-benzothiazole methiodide, 0.2 g ethyl orthoformate and 3 ml pyridine were boiled for 20 minutes. After cooling, the precipitated dye was filtered and crystallized from alcohol. Violet needles, m.p. 264-266°. Yield 0.07 g (44%).

Found %: I 22.23, 22,20. $C_{27}H_{33}N_2S_2I$. Calculated %: I 22.30.

Bis-[3-methyl-6-tert.butylbenzothiazole (2)] trimethinecyanine perchlorate —14. 0.1 g 2-methyl-6-tert. butylbenzothiazole methyl perchlorate, 0.1 g ethyl orthoformate and 2 ml pyridine were boiled for 20 minutes. The dye was precipitated with ether, filtered and crystallized from alcohol. Violet needles, m.p. 263° with decomp. Yield 0.04 g (47%).

Found %: S 11.67, 11.40. $C_{27}H_{33}N_2O_4SCl$. Calculated %: S 11.66.

SUMMARY

1. The influence of steric hindrance on the auxochromic action of the dimethylamino group in tetra-substituted thiacarbocyanines was studied. It was established that the introduction of a methyl or a tertiary butyl group in the ortho-position to the dimethylamino group partly suppresses the latter's auxochromic action, the tertiary butyl group exerting a greater influence than the methyl group.

2. Nine new benzothiazole derivatives and fourteen new thiacarbocyanines were synthesized.

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Received November 17, 1952

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INVESTIGATION OF THE STRUCTURE OF THE ALKALOID SONGORINE

PREPARATION OF ACONITANE – THE OXYGEN-FREE HETEROCYCLIC NUCLEUS OF SONGORINE

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A comparison of the compositions of various aconite alkaloids by A. P. Orekhov and R. A. Konovalova [1] led these authors to suggest that they are all derivatives of one and the same heterocyclic ring and only differ in the number and distribution of the substituents and in the presence of double bonds. The authors attempted to prepare such a heterocyclic ring of the alkaloid Talatisine, but the research did not lead to the desired result.

Some successes in the investigation of cyclic systems constituting the molecule of aconite alkaloids were achieved by using the method of selenium dehydrogenation. Hetisine, atisine, napelline and staphisine gave neutral fractions from which phenanthrene hydrocarbons were isolated [2]: from hetisine was got pimanthrene (1,7-dimethylphenanthrene); from atisine, 1-methylphenanthrene and 1-methyl-6-ethylphenanthrene; from staphisine, phenanthrene, pimanthrene and 3-methylretene (1,3-dimethyl-7-isopropylphenanthrene).

On the basis of the formation of phenanthrene homologs, in particular of pimanthrene and 3-methylretene, it was concluded that this group of alkaloids was related to the resin acids in the sense that the basis of the molecules of the aconite alkaloids is a pentacyclic structure, part of which is the perhydrophenanthrene ring condensed with a bicyclic, nitrogen-containing system.

In this paper we present the first results of our study of the structure of the alkaloid songorine, discovered by S. Yu. Yunusov [3].

Songorine $C_{21}H_{29}O_3N$ contains two hydroxyl and one carbonyl group; it has a double bond. From the standpoint that it was first necessary to establish the nature and location in the molecule of the rings in which the nitrogen atom is linked, we started our investigation with the aim of preparing the oxygen-free heterocyclic ring of the alkaloid in order to be able subsequently to effect its Hofmann degradation and to investigate the unsaturated nitrogen-free substance.

Songorine with m.p. 201-202° and specific rotation $[\alpha]_D$ −135.4° was prepared from Aconitum songoricum. Its constants correspond to those in the literature. The hydroxyl groups of songorine were replaced by chlorine by reaction with phosphorus oxychloride. The chlorine derivative (without purification and isolation in the individual state) was subjected to catalytic reduction with skeletal nickel catalyst at a small excess pressure of hydrogen in presence of two equivalents of caustic alkali. An amino ketone was obtained with the composition $C_{21}H_{31}ON$ for which we propose the name of oxoaconitane. The base is a colorless crystalline substance with m.p. 64-66°; its hydrochloride has the composition $C_{21}H_{31}ON \cdot HCl$, m.p. 293°; $[\alpha]_D$ −76.3°; hydrobromide $C_{21}H_{31}ON \cdot HBr$, m.p. 299°, $[\alpha]_D$ −69.7°. Both salts are well-crystallized, soluble in alcohol, poorly soluble in acetone and water.

The carbonyl group of oxoaconitane was reduced by $LiAlH_4$ to give the amino alcohol hydroxyaconitane $C_{21}H_{33}ON$, m.p. 151.5°; $[\alpha]_D$ −38.6°.

Elimination of the hydroxy group of hydroxyaconitane with formation of the oxygen-free substance $C_{21}H_{33}N$ was effected as in the removal of the hydroxy groups from songorine: substitution with chlorine by the action of phosphorous oxychloride followed by reduction over skeletal nickel catalyst.

Aconitane is the saturated, oxygen-free heterocyclic nucleus of the alkaloid songorine. The base $C_{21}H_{33}N$ melts at 69.5-70°, rotates the plane of polarization of light to the left ($[\alpha]_D$ −50.3°), and distils in vacuum at 170-180° (3 mm). Aconitane hydrochloride has the composition $C_{21}H_{33}N \cdot HCl$, m.p. 275°, $[\alpha]_D$ −37.2°. Hydrobromide $C_{21}H_{33}N \cdot HBr$, m.p. 282-283°, $[\alpha]_D$ −29.4°.

EXPERIMENTAL

(assisted by R. L. Bogomazova)

Preparation of Oxoaconitane

To 10 g songorine with ice cooling was added 100 ml phosphorus oxychloride. The reaction mass was gradually brought to the boil over a gauze and boiled for 2 hours, after which the excess of phosphorus oxychloride was distilled off in vacuum. The residue was treated with water, at first with ice cooling and later while heating on the boiling water bath and being intensively shaken until solution was complete. The aqueous solution was made alkaline with concentrated aqueous ammonia and extracted with ether. The ether extract was dried with potassium carbonate and the ether was distilled off to leave 10.5 g of a colorless oil which was dissolved in 300 ml 80% ethyl alcohol. To the alcoholic solution was added 6 ml 40% NaOH solution and 15 g skeletal nickel catalyst, and the whole was shaken under slight excess pressure in a hydrogen atmosphere. In the course of 16 hours 1750 ml (2.7 moles) hydrogen was absorbed, after which absorption ceased. The solution was filtered from catalyst, acidified with hydrochloric acid and evaporated in a vacuum. Addition of water to the oily residue brought down oxoaconitane hydrochloride which was sparingly soluble in water and after recrystallization from water weighed 2.8 g and melted at 293°. After a second crystallization the yield was 1.7 g with the same melting point.

0.0819 g substance in 10 ml 0.5% HCl, l = 1 dm, α_D −0.63°, $[\alpha]_D$ −76.9°.

3.879 mg substance: 10.349 mg CO_2, 3.163 mg H_2O. 10.172 mg substance: 0.353 ml N_2 (24°, 729 mm). Found %: C 72.94; H 9.12; N 3.82. $C_{21}H_{31}ON \cdot HCl$. Calculated %: C 72.06; H 9.22; N 4.02.

The base was prepared by stirring 1.7 g of the hydrochloride with water, making the suspension alkaline with aqueous ammonia and extracting with ether. The ether extract was dried with potassium carbonate and the ether was driven off to leave the colorless crystalline base, m.p. 64-66°, readily soluble in ether, pentane, alcohol, acetone, chloroform and benzene; sparingly soluble in water. The substance could not be recrystallized. The hydrobromide of oxoaconitane was prepared in the form of fine needlets by triturating the base with 5% aqueous HBr and crystallizing from hot alcohol with addition of an equal volume of ether. M.p. 299°. 0.1019 g substance in 10 ml water, l = 1 dm, α_D −0.71°, $[\alpha]_D$ −69.7°.

3.372 mg substance: 7.960 mg CO_2, 2.501 mg H_2O. 3.392 mg substance: 7.996 mg CO_2, 2.539 mg H_2O. 10.281 mg substance: 0.295 ml N_2 (23°, 740 mm). 10.890 mg substance: 0.309 ml N_2 (23°, 738 mm). 4.542 mg substance: 2.191 mg AgBr. Found %: C 64.42, 64.33; H 8.30, 8.37; N 3.22, 3.18; Br 20.53. $C_{21}H_{31}ON \cdot HBr$. Calculated %: C 63.95; H 8.18; N 3.55; Br 20.26.

The mother liquor from the hydrochloride of the base was made alkaline with aqueous ammonia and extracted with ether. After drying the ether extract with potassium carbonate and driving off the ether, 6.0 g of colorless oil was obtained from which we only succeeded in isolating oxoaconitane by chromatography: 6 g of the substance in 60 ml ether; solution passed through a column containing a bed of 75 g activated alumina moistened with wet ether; height of bed 70 cm. After passage of the whole of the solution, the sorbent in the column was washed with ether. From the instant of commencement of emergence of the bases from the column, determined by the reaction with silicotungstic acid, 30 ml fractions of eluate were collected. Distillation of the solvent from the second to the fourth fractions gave 2.1 g crystallizable substance, trituration of which with 5% aqueous HBr gave 1.8 g crystalline hydrobromide melting at 298° (from alcohol-ether) and not causing a melting point depression in admixture with the previously isolated hydrobromide of oxoaconitane. 0.1077 g substance: 10 ml water, l = 1 dm, α_D −0.75, $[\alpha]_D$ −69.6°.

Preparation of Hydroxyaconitane

2.5 g oxoaconitane and 1.0 g $LiAlH_4$ were dissolved in 800 ml absolute ether and refluxed four hours. The solvent was then distilled off to the extent of two-thirds of its volume, the reaction mass was treated with 10% aqueous HCl until the precipitate formed at the start of the addition had redissolved; the aqueous acid layer was separated, the ether layer was extracted 3 times with 10% HCl. The aqueous acid extracts were combined, made alkaline with 40% NaOH and extracted with ether. Drying of the ether extract with potassium carbonate and distillation of the solvent gave 2.35 g partly crystallizing residue which was treated with pentane. The oil then went into solution, leaving a residue of colorless needles. The latter were drained and further purified by crystallization from acetone and then from alcohol. Yield 0.9 g colorless needles melting at 151.5-153°. 0.0881 g substance: 10 ml alcohol, l = 1 dm, α_D −0.34, $[\alpha]_D$ −38.6°.

4.064 mg substance: 12.049 mg CO_2, 3.740 mg H_2O. 10.567 mg substance: 0.395 ml N_2 (24° 738 mm). Found %: C 80.91; H 10.30; N 4.17. $C_{21}H_{33}ON$. Calculated %: C 79.94; H 10.54; N 4.44. 0.0113 g substance: 0.0989 g camphor: Δt 15.0 and 14.0° in two experiments. Found: M 305 and 327. $C_{21}H_{33}ON$. Calculated: M 315.

Preparation of Aconitane

To 0.8 g hydroxyaconitane, with ice cooling, was added 8 ml phosphorus oxychloride; the reaction mass was gradually brought to the boil on a gauze and refluxed 2 hours. The excess of phosphorus oxychloride was distilled off in vacuum and the residue was worked up with water, at first with ice-cooling and then on the boiling water bath; the oil was seen to dissolve and a colorless crystalline substance came out. The suspension was made alkaline with aqueous ammonia and extracted with ether. After drying the extract with potassium carbonate and distilling off the ether, a slightly colored liquid base was obtained which was dissolved in 80 ml alcohol. To the alcoholic solution was added 1.5 g skeletal nickel catalyst and the whole was shaken at a slight excess pressure in a hydrogen atmosphere. Absorption was completed in 8 hours. The alcoholic solution was filtered from catalyst, acidified with hydrochloric acid and evaporated in vacuum. The colorless crystalline residue of the hydrochloride was recrystallized by adding ether to its alcoholic solution. Yield 0.5 g fine, colorless needles, melting at 275° with partial sublimation. 0.0915 g substance: 10 ml alcohol, l = 1 dm α_D −0.34°, $[\alpha]_D$ −37.2°.

The specific rotation did not change after recrystallization.

3.557 mg substance: 9.733 mg CO_2; 3.110 mg H_2O. 3.318 mg substance: 9.104 mg CO_2; 2.958 mg H_2O. 8.500 mg substance: 0.304 mg N_2 (26°, 725 mm). 8.498 mg substance: 0.295 ml N_2 (26°, 725 mm). Found %: C 74.67, 74.88; H 9.78, 9.97; N 3.89, 3.78. $C_{21}H_{33}N \cdot HCl$. Calculated %: C 75.05; H 10.20; N 4.17.

The base was obtained by treating the aqueous solution of the hydrochloride with aqueous ammonia and extracting with ether. After drying the extract with potassium carbonate and driving off the solvent, oily base was obtained which crystallized when rubbed with a glass rod. Crystallization from acetone gave colorless needles melting at 69.5-70°. The m.p. was unchanged after recrystallization. The compound is readily soluble in pentane, benzene, ether, chloroform, less readily soluble in alcohol and acetone, poorly soluble in water; it distils in vacuum without decomposition at 170-180° (3 mm). 9.540 mg substance: 1 ml alcohol, l = 0.5 dm, α_D −0.24°, $[\alpha]_D$ −50.3°.

4.053 mg substance: 12.608 mg CO_2; 4.058 mg H_2O. 4.921 mg substance: 15.241 mg CO_2; 4.916 mg H_2O. 8.750 mg substance: 0.331 mg N_2 (26°, 735 mm). 8.704 mg substance: 0.353 ml N_2 (26°, 735 mm). Found %: C 84.89, 84.52, H 11.20, 11.18; N 4.17, 4.47. $C_{21}H_{33}N$. Calculated %: C 84.21; H 11.11; N 4.68. 4.460 mg substance; 59.5 mg camphor: Δt 10.5 and 10.0° in two experiments. Found: M 286 and 300. $C_{21}H_{33}N$. Calculated: M 299.

The hydrobromide was obtained by triturating the base with 5% aqueous HBr. After recrystallization from alcohol-ether, the salt melted at 282-283°; no change after a second crystallization.

10.021 mg substance: 1 ml alcohol, l = 0.5 dm, α_D −0.15°, $[\alpha]_D$ −29.4°.

3.882 mg substance: 9.533 mg CO_2; 3.030 mg H_2O. 4.195 mg substance: 10.300 mg CO_2; 3.311 mg H_2O. 9.085 mg substance: 0.307 ml N_2 (26°, 732 mm). 10.415 mg substance: 0.324 ml N_2 (26°, 732 mm). Found %: C 67.01, 67.00, H 8.73, 8.83, N 3.71, 3.42. $C_{21}H_{33}N \cdot HBr$. Calculated %: C 66.30; H 9.00; N 3.68.

SUMMARY

From songorine $C_{27}H_{45}O_5N$ were prepared the previously unknown amino ketone oxoaconitane $C_{21}H_{31}ON$, the amino alcohol hydroxyaconitane $C_{21}H_{33}ON$ and the oxygen-free substance aconitane $C_{21}H_{33}N$.

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Received July 11, 1952

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THE STRUCTURE OF THE POLYAMIDES OF DIPHENIC ACID

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The polyamides formed by diphenic acid and hexamethylenetetramine are transparent, light-yellow resins, soluble in m-cresol, alcohol-benzene and glacial acetic acid. The resins with a molecular weight of 10,000 have a m.p. of 170-175°. Due to the fact that the structure of high-molecular compounds considerably influences their physical properties, it was of interest to establish to what extent the molecular chains of polyamide prepared from diphenic acid and hexamethylenetetramine were oriented. For the purpose of studying the polyamide structure, polyhexamethylenediphenamide and (for comparison) polyhexamethyleneadipamide were synthesized.

The reaction conditions for the preparation of polyhexamethylenediphenamide were as follows: The neutral salt of diphenic acid and hexamethylenediamine was placed in a flask heated on a metal bath. The bath temperature was regulated by a contact thermometer and checked by a mercury thermometer immersed in the reaction mixture. The reaction was performed at a temperature of 220° for 2 hours under a reflux condenser then for four hours without the condenser while distilling off reaction products, and for two hours in a 10-15 mm vacuum at the same temperature. Nitrogen (purified from oxygen traces) was passed through the reaction mixture during the experiment.

Polyhexamethyleneadipamide was synthesized by the known procedure.*

The prepared polyhexamethylenediphenamide had m.p. 170-175°; the polyhexamethyleneadipamide had m.p. 248-250°.

Filaments with a diameter of about 1 mm were drawn out from the polyamides and X-ray diagrams were prepared,** using a "Mikro" apparatus. Exposure 50 milliampere hours.

Double-sided Debyeograms were obtained, on which could be measured the distances (21) between symmetrically distributed diffraction patterns. Knowing the radius of the cylindrical camera (2R = 57.4 mm), we could determine, from the measured distances, the deviation angle θ for each diffraction pattern ($\theta = \frac{1}{2R}$). From these angles was determined the value (d) of the interplanar distances (for the Debye lines) or the mean distance (d') between the scattering centers (for diffusion haloes) by the usual formula (for $\lambda = 1.537$ A).

The X-ray diagram prepared from polyhexamethylenediphenamide contains only diffusion haloes characterized by the magnitudes presented in Table 1.

The X-ray diagram prepared from hexamethyleneadipamide contains, apart from diffusion haloes one of which is resolved into two very similar independent haloes, four relatively weak and diffuse Debye lines. The data characterizing these haloes are set out in Table 2.

TABLE 1

θ	d' (A)	Maximum error Δd (A) with a measuring error of ± 0.2 mm
6°00'	7.361	0.25
10°31'	4.216	0.12
21°24'	2.109	0.018

The data that have been obtained show that polyhexamethylenediphenamide has a definitely amorphous structure. This amorphous structure is evidently due to the distribution of the carboxyl groups in diphenic acid not being favorable to orientation of the polyamide chains.

The X-Ray diagrams of the polyamides are shown in figures 1 and 2.

* See V. V. Korshak and S. R. Rafikov. Synthesis and Investigation of High-Molecular Compounds, p. 240 (1949).

** The X-ray work was carried out in the laboratory of physical metallurgy by Doctor V. I. Arkharov and assistant Z. P. Kichigina to whom we convey our thanks.

Fig. 1. X-Ray diagram of polyhexamethylenediphenamide.

Fig. 2. X-Ray diagram of polyhexamethylenediparnide.

TABLE 2

θ	d	Intensity and diffusivity
6°22'	6.939	Moderate
10°00'	4.431	Very strong diffusion
11°59'	3.705	Very strong diffusion
18°56'	2.372	Weak
20°48'	2.167	Weak, strongly diffused
22°45'	1.990	Very weak, strongly diffused
31°27'	1.475	Very weak, strongly diffused
40°03'	1.196	Very weak, strongly diffused

SUMMARY

It has been established that polyhexamethylenediphenamide possesses an amorphous structure.

Received June 27, 1951

Ural Branch of the Academy of Sciences of the USSR

SYNTHESIS OF DERIVATIVES OF 3,4'-ACE-1,2-BENZANTHRACENE WITH THE HELP OF LITHIUM REAGENTS

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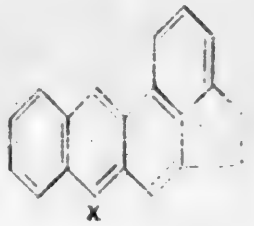
Homologs of 3,4'-ace-1,2-benzanthracene are of interest because of their ability to induce malignant neoplasms [1]; one of us synthesized them [2] by reaction of organomagnesium compounds with 3,4'-ace-1,2-benzanthrone-10. The yields of hydrocarbons did not exceed 21-30% of the theoretical by this route.

In the present communication we describe a method of preparation of alkyl and other functional derivatives of 3,4'-ace-1,2-benzanthracene with substituents in the 10 position, based on the use of organolithium compounds [3]. The starting organolithium compound of 3,4'-ace-1,2-benzanthracene, which readily exchanges the metal for diverse radicals, is smoothly prepared by the action of n-butyllithium or of phenyllithium on 10-bromo-3,4'-ace-1,2-benzanthracene.

Replacement of bromine by lithium in 10-bromo-3,4'-ace-1,2-benzanthracene proceeds much more slowly with phenyllithium than with n-butyllithium. In the former case the reaction is completed after an hour, whereas with n-butyllithium it is completed in a few minutes.

The reaction between 3,4'-ace-1,2-benzanthryl-10-lithium and alkyl halides proceeds more or less readily depending on their nature. The reaction proceeds the most readily with methyl iodide, giving 10-methyl-3,4'-ace-1,2-benzanthracene (I) in 72% yield. Reaction between 3,4'-ace-1,2-benzanthryl-10-lithium and higher alkyl halides (ethyl iodide and n-butyl iodide) proceeds much more slowly and calls for heating for about 40 hours at 40° in order to complete it (II and III).

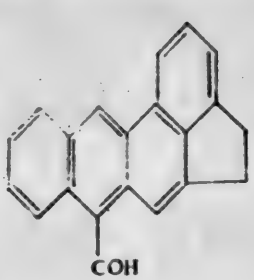
In the carboxylation of 3,4'-ace-1,2-benzanthryl-10-lithium prepared with the help of n-butyllithium or phenyllithium, from 8 to 20% of the 3,4'-ace-1,2-benzanthracene is recovered unchanged side by side with the carboxylic acid (IV) (40% yield). It was established that the hydrocarbon is formed during the very process of carboxylation and is not a consequence of reaction between the organolithium compound and the ether, toward which 3,4'-ace-1,2-benzanthryl-10-lithium is very stable.



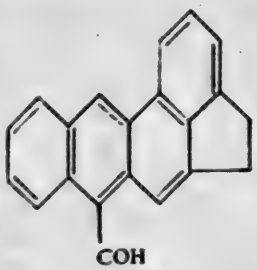
X = CH_3 (I), C_2H_5 (II), n-C_4H_9 (III), $COOH$ (IV), $COOC_2H_5$ (V), CH_2CH_2OH (VI).

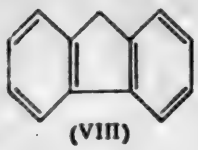
Reaction of the starting organolithium compound with ethyl chloroformate or ethylene oxide gives the corresponding ethyl ester of 3,4'-ace-1,2-benzanthracene-10-carboxylic acid (V) and 10-β-hydroxyethyl-3,4'-ace-1,2-benzanthracene (VI).

With non-enolizing ketones the lithium compound of 3,4'-ace-1,2-benzanthracene gives tertiary alcohols. Benzophenone gave 3,4'-ace-1,2-benzanthryl-10-diphenylcarbinol (VII), fluorenone gave 3,4'-ace-1,2-benzanthryl-10-fluorenol (VIII):



(VII)





(VIII)

EXPERIMENTAL

10-Methyl-3,4'-ace-1,2-benzanthracene (I). To an ethereal solution of n-butyllithium, prepared by the usual method [3] from 0.5 g n-butyl chloride, 0.1 g metallic lithium and 10 ml absolute ether, is added a solution of 1 g of 10-bromo-3,4'-ace,1,2-benzanthracene in 15 ml dry benzene (thiophene-free). After 10 minutes, addition is made to the reaction mass of an ethereal solution of 1.3 g methyl iodide. The mass is heated for 2 hours at 40° and treated with water; the solvents are distilled off and the crystalline residue is twice recrystallized from a mixture of benzene and ethanol to give 0.58 g light-yellow crystals melting at 181-182° and not depressing the melting point of a specimen of 10-methyl-3,4'-ace,1,2-benzanthracene prepared by another route [2]. Yield 72.5% of the theoretical.

10-Ethyl-3,4'-ace-1,2-benzanthracene (II). To 3,4'-ace-1,2-benzanthryl-10-lithium, prepared by the above-described method from 1 g of the bromo-compound, was added 1.4 g ethyl iodide, and the reaction mass was heated for 40 hours at 40°.

After the reaction mixture had been worked up in the usual way, the ether-benzene layer yielded a resinous product from which was obtained, by crystallization from benzene-petroleum ether, 0.34 g substance melting at 168-171° (40.1% of theory).

After a fresh crystallization from the same solvents, the m.p. was 174-175° and there was no depression in admixture with a specimen of 10-ethyl-3,4'-ace-1,2-benzanthracene [2]. 3,4'-Ace-1,2-benzanthracene was not detected among the reaction products.

Heating for 3 hours gave 13% of 10-ethyl-3,4'-ace-1,2-benzanthracene.

10-n-Butyl-3,4'-ace-1,2-benzanthracene (III). To 3,4'-ace-1,2-benzanthryl-10-lithium, prepared from 1 g 10-bromo-3,4'-ace-1,2-benzanthracene, was added 2.5 g n-butyl iodide. The mixture was heated for 40 hours at 40°. From the reaction products was isolated a hydrocarbon (0.57 g) with m.p. 122-128° (60.3% of the theoretical). After recrystallization from benzene-ethanol, the substance melted at 127-128° and did not depress the m.p. in admixture with a specimen of 10-n-butyl-3,4'-ace-1,2-benzanthracene [2]. When the reaction period was cut down to 20 hours, the products isolated were 0.19 g 10-n-butyl-3,4'-ace-1,2-benzanthracene with m.p. 121-130° (41% of the theoretical) and 0.05 g 3,4'-ace-1,2-benzanthracene (13%), formed by hydrolysis of the original organolithium compound not entering into reaction.

3,4'-Ace-1,2-benzanthracene 10-carboxylic acid (IV).

a) Using n-butyllithium. To an ethereal solution of n-butyllithium, prepared from 0.5 g n-butyl chloride and 0.1 g lithium metal, was added a benzene solution of 1 g 10-bromo-3,4'-ace-1,2-benzanthracene (15 ml). After 10 minutes the reaction mixture was poured on to solid carbon dioxide, then water was added, and the precipitate was filtered and treated with hot caustic alkali solution; the alkaline filtrate was combined with the main aqueous layer. Acidification yielded 0.52 g 3,4'-ace-1,2-benzanthracene-10-carboxylic acid, melting at 229-230° (with decomp.). Yield 58.2% of the theoretical.

After crystallization from ethanol, the acid forms long, yellow needles melting at 236-237° (with decomposition).

5.257 mg substance: 16.304 mg CO_2; 2.304 mg H_2O. Found %: C 84.63; H 4.90. $C_{21}H_{14}O_2$. Calculated %: C 84.54; H 4.73.

From the ether-benzene layer was separated 0.03 g of a light-yellow, crystalline substance which after crystallization from benzene had m.p. 191-192° and did not depress the m.p. in admixture with 3,4'-ace-1,2-benzanthracene.

b) Using phenyllithium. To an ethereal solution of phenyllithium (0.002 mole) was added a benzene solution of 0.5 10-bromo-3 4'-ace-1,2-benzanthracene (0.0015 mole). After reaction for 10 minutes, the products of reaction were carboxylated by the usual method. 0.05 g 3 4'-ace-1,2-benzanthracene-10-carboxylic acid (11% of theory) and 0.33 g of the original bromo compound (60% of the amount taken) were obtained. On increasing the duration of reaction to 1½ hours, the yields were 0.19 g acid (42.7% of theory) and 0.08 g 3,4'-ace-1,2-benzanthracene (21% of theory).

The same results were obtained when the duration of the reaction between phenyllithium and the bromo compound was raised to 3-5 hours. Nor did the picture change when the amount of phenyllithium was increased to 3 equivalents.

Ethyl ester of 3 4'-ace-1 2 benzanthracene-10-carboxylic acid (V). Reaction of an ether-benzene solution of 3,4'-ace-1,2-benzanthryl-10-lithium, prepared from 0.5 g 10-bromo-3,4'-ace-1,2-benzanthracene and n-butyllithium, with 0.2 g ethyl monochloroformate gave a yellow crystalline product, melting after crystallization from a mixture of benzene and petroleum ether at 161-177°. After recrystallization from the same solvents, 0.26 g of the ethyl ester of 3,4'-ace-1,2-benzanthracene-10-carboxylic acid was obtained with m.p. 180.2-182.5° (yield 53.5% of the theoretical). After one more recrystallization the compound melted at 182.5-184.5°.

4.462 mg substance: 13.823 mg CO_2; 2.300 mg H_2O. Found %. C 84.54; H 5.76. $C_{23}H_{18}O_2$. Calculated %: C 84.66; H 5.52.

From the main mother liquor was isolated 0.025 g 3,4'-ace-1,2-benzanthracene (m.p. 189-191°).

10-β-Hydroxyethyl-3 4'-ace-1 2-benzanthracene (VI). Into an ether-benzene solution of 3,4'-ace- 1,2-benzanthryl-10-lithium, prepared from 1 g 10-bromo-3,4'-ace-1,2-benzanthracene, was passed an excess of gaseous ethylene oxide. Heat was developed and a white, flocculent precipitate of lithium alcoholate was formed. The latter was decomposed and 0.44 g of a substance with m.p. 187.5-189° was filtered off. The ether-benzene solution yielded 0.19 g substance with m.p. 184-187°. Crystallization of the combined precipitates from ethylacetoacetate gave 0.56 g (63% of the theoretical) of 10-β-hydroxyethyl 3,4'-ace 1,2-benzanthracene in the form of yellow, fluffy needlets melting at 189.5-190.5°.

3.888 mg substance: 12.614 mg CO_2; 2.139 mg H_2O. Found %: C 88.53; H 6.15. $C_{22}H_{18}O$. Calculated %: C 88.56; H 6.08.

3,4'-Ace-1,2-benzanthryl-10-diphenylcarbinol (VII). To an ether-benzene solution of 3,4'-ace-1,2-benzanthryl-10-lithium, prepared from 1 g 10-bromo-3,4'-ace-1 2-benzanthracene and n-butyllithium, was added 0.55 g benzophenone. After 2 hours, water was added to the reaction mixture, the solvents were distilled off and the residue crystallized from isoamyl ether, to give 0.84 g yellow powder, melting at 189-192° (with decomp.). Yield 64.1% of the theoretical.

Recrystallization from the same solvent gave 0.50 g 3,4'-ace-1,2-benzanthryl-10-diphenylcarbinol in the form of long prisms melting at 193-193.5° (with decomp.).

7.312 mg substance: 24.306 mg CO_2; 3.720 mg H_2O. Found %: C 90.71; H 5.69. $C_{33}H_{24}O$. Calculated %: C 90.78; H 5.54.

3,4'-Ace-1,2-benzanthryl-10-fluorenol (VIII). To a solution of 3,4'-ace-1,2-benzanthryl-10-lithium, prepared from 0.5 g 10-bromo-3,4'-ace-1,2-benzanthracene and n-butyllithium, was added an ethereal solution of 0.28 g fluorenone. Slight heat was developed and the color became lighter. After working up as usual, the oily residue was crystallized from isoamyl ether. 0.46 g yellow powder with m.p. 230-231° was isolated, representing 70.7% of the theoretical yield. After two crystallizations from acetone it formed stout, light-yellow needles of 3,4'-ace-1,2-benzanthryl-10-fluorenol, melting at 234.5-235°.

5.814 mg substance. 19.430 mg CO_2; 2.681 mg H_2O. Found %: C 91.20. H 5.16. $C_{33}H_{22}O$. Calculated %. C 91.21. H 5.10.

SUMMARY

Reaction of n-butyllithium or phenyllithium with 10-bromo-3,4'-ace-1,2-benzanthracene gives 3,4'-ace-1,2-benzanthryl-10-lithium, which can be successfully used for synthesis of homologs and oxygenated derivatives of 3,4'-ace-1,2-benzanthracene.

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Received July 21, 1951

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SPECTROPHOTOMETRY OF BIURET COMPLEXES AS A METHOD OF INVESTIGATION OF PROTEINS AND PEPTIDES

XVII. DIRECTION OF ENOLIZATION DURING THE BIURET REACTION OF PROTEINS AND PEPTIDES

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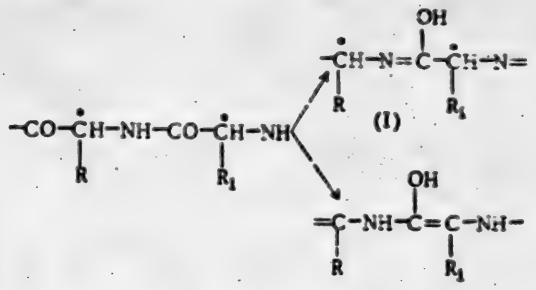
The necessity for a strongly alkaline medium for the formation of biuret complexes gives reason to believe that enolization must occur in this reaction. This is supported by Rising's observation [1] that substituted phthalimide and succinimide, in which there is no possibility of enolization, do not form a biuret complex. But whereas in the case of diamides and imino acids only one direction of enolization is possible, there are two possible directions of the reaction with peptides and proteins:



(II)

Although Rising ruled out the possibility of the N-enolic form of the peptide bond in the structure of the biuret complex of triglycylglycine, he did not experimentally demonstrate the correctness of this hypothesis.

Since we considered the N-enolic form of the peptide bonds to be the most probable in the biuret reaction of peptides and proteins, we considered an experimental proof of this feature of the structure of the complex desirable.

1. Effect of the Biuret Reaction on the Optical Activity of Peptides and Protein

On comparing formulas (I) and (II) we can observe that carbon-carbon enolization (direction II) must lead to loss of the optical activity of a polypeptide and protein. On the other hand, enolization of the peptide bond in accordance with scheme I does not modify the optical activity of the substance. In the light of these considerations we based our investigations on a study of the optical activity of synthetic polypeptides and proteins during formation of the biuret complexes. As synthetic models we used optically active alanine di- and tripeptides which were synthesized essentially by Bergman's method. (Details in experimental part). Proteins taken for investigation were casein, gelatin and serum albumen. 1% solutions of proteins and peptides were prepared and the rotation of the plane of polarization by these solutions was measured. Solutions of the copper and nickel biuret complexes were also prepared. In the case of the nickel complexes, the rotation measurements were performed on the solutions of the complexes themselves. The solutions of the copper complexes were so intensely colored that they were not amenable to measurement, and the rotation was determined after breakdown of the complex by acidification.

Results presented in Table 1. The following points emerge on examining the data of this table:

1) Formation of nickel biuret complexes both by proteins and polypeptides in the majority of cases does not change the magnitude of the rotation of the plane of polarization (column 4). The rotation of the nickel biuret complex of the alanine tripeptide is higher than the rotation of the free alanine tripeptide. The insignificant fall in the rotation of the solution of the casein complex is within the limit of experimental error.

2) Formation of a complex contributes to the constancy of the optical activity of proteins and peptides and hinders racemization under the influence of alkalies. Even after standing for 24 hours the rotation of solutions of biuret complexes of proteins and peptides does not change (column 4). On the other hand, after standing with alkali for 24 hours, the solutions of the free proteins and peptides undergo considerable racemization (column 3).

TABLE 1

Optical Activity of Peptides and Proteins after Formation of Biuret Complexes

Substance examined	1	2	3	4	
	Conc. of solution (%)	Rotation of solution $[\alpha]_D^{20}$	Rotation of solution with addition of alkali after 24 hours	Rotation of Ni-biuret complex of the substance after	
				2 hours	24 hours
Casein	1	−1.15	−0.65	−0.95	−0.98
Gelatin	1	−1.4	−0.75	−1.4	−1.45
Serum albumen	1	−0.67	−0.5	−0.62	−0.62
Carbobenzoxy-l-alanyl-l-alanine	1.5	−0.62	−0.4	−0.6	−0.6
l-Alanyl-l-alanine	2	−0.5	−0.35	−0.55	−0.55
Carbobenzoxy-l-alanyl-l-alanyl-l-alanine	1	−0.75	−0.51	−0.98	−0.98
l-Alanyl-l-alanyl-l-alanine	1.25	−0.58	−0.38	−1.0	−1.0

3) After decomposing the biuret complexes of proteins and peptides with hydrochloric acid, we observed a considerable decline of the optical activity of both proteins and peptides (columns 5 and 7). Cases are reported in the literature of a considerable effect being exerted by salts and acids on the optical activity of protein solutions [2,3]. It was necessary to check whether there was a marked drop in the optical activity of solutions of proteins and peptides as a result of addition of acid and of a nickel or copper salt (which was formed after decomposition of the complex). For this purpose the rotation was measured with solutions of free proteins with additions of hydrochloric acid and nickel nitrate or copper acetate in the same concentration as was present after decomposition of the complexes (columns 6 and 8). It was found that the magnitude of the rotation with solutions of proteins with additions of hydrochloric acid and salts was the same as that with solutions of proteins after decomposition of the complex (both the nickel and the copper complex). Consequently the fall in rotation with protein solutions observed after decomposition of the complex is the result of addition of hydrochloric acid and the formation of a salt, and is not the result of racemization.

All the above observations lead indisputably to the conclusion that racemization does not take place during the biuret reaction of proteins and peptides and that consequently, enolization of the peptide bonds occurs. We are therefore justified in representing the peptide bonds in the enol form in the structure of the biuret complex of proteins and peptides.

2. Influence of Optical Isomerism of Peptides on the Formation of the Biuret Complex

In a previous communication one of us showed the influence of various amino acids on the character of the complex formation of peptides. But the question of the influence of the optical isomerism of amino acids on the biuret reaction of peptides has not previously been considered. In view of the fact that natural compounds contain optically active amino acids, it is necessary to establish whether the optical activity of the amino acids also has some influence on the character of complex formation of peptides. With this aim we synthesized alanine di- and tripeptides into whose composition entered both the natural l-form of alanine and the synthetic d-form. For comparison, we also synthesized the racemic alanine di- and tripeptides.

In Tables 2 and 3 and Figures 1 and 2 are presented the results of spectrophotometric measurements of high absorption by the copper biuret complexes of alanine di- and tripeptides.

Table 2 and Fig. 1 show that the character of the absorption of the complex of the racemic tripeptide is similar to the absorption of optically active l-alanyl-l-alanyl-l-alanine and of the tripeptide containing the d-form (l-alanyl-d-alanyl-l-alanine). The position of the maximum in all three complexes is at one and the same wave-length of 570 mμ. The intensity of absorption throughout the whole of the visible portion of the spectrum is very similar in all three complexes.

The spectrophotometric investigation of the light absorption by complexes of alanyl dipeptides and their carbobenzoxy derivatives showed that the complex of the optically active l-alanyl-l-alanine has an absorption character very similar to that observed by us for the complex of racemic alanylalanine. The absorption maximum with complexes of alanyl dipeptides lies at a wave length of 680 mμ, and with complexes of the carbobenzoxy derivatives of 660 mμ. The results provide evidence that the character of the absorption in the visible region

5	6	7	8
Rotation after breakown of Ni-complex	Rotation of test solution with addition of $Ni(NO_3)_2$ and HCl	Rotation after breakdown of Cu-biuret complex	Rotation of solution with addition of $Cu(CH_3COO)_2$ and HCl
−0.51	−0.50	−	−
−0.68	−0.75	−0.82	−0.85
−0.6	−0.58	−	−
−0.58	−	−	−
−0.53	−	−	−
−0.72	−	−	−
−0.56	−	−	−

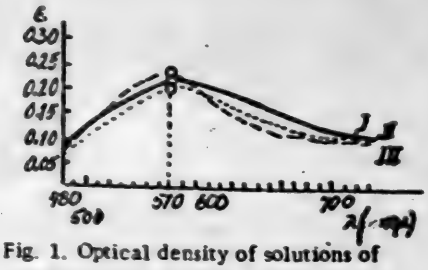


Fig. 1. Optical density of solutions of copper biuret complexes of tripeptides (M./300). 1) l-Alanyl-d-alanyl-l-alanine; II) l-alanyl-l-alanyl-l-alanine; III) racemic dialanylalanine.

TABLE 2

Magnitudes of Optical Densities ε of Copper Biuret Complexes of Tripeptides (Tripeptide Concentration M./150)

λ (in mμ)	Racemic alanylalanyl-alanine	l-Alanyl-l-alanyl-l-alanine	l-Alanyl-d-alanyl-l-alanine
480	0.0642	0.0630	0.0807
500	0.1202	0.1138	0.1263
520	0.1746	0.1494	0.1601
540	0.2189	0.1752	0.1909
550	0.2251	0.1861	0.2075
560	0.2290	0.1984	0.2156
570	0.2346	0.2170	0.2249
580	0.2180	0.2005	0.2150
590	0.2042	0.1990	0.2071
600	0.1822	0.1895	0.2008
620	0.1608	0.1751	0.1910
640	0.1469	0.1523	0.1731
660	0.1256	0.1342	0.1587
680	0.1172	0.1258	0.1377
700	0.1091	0.1184	0.1241
730	0.1065	0.1021	0.1104

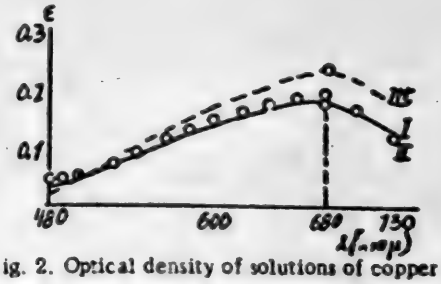


Fig. 2. Optical density of solutions of copper biuret complexes of dipeptides (M./150). 1) Racemic alanylalanine; II) l-alanyl-l-alanine; III) d-alanyl-l-alanine.

of the spectrum by biuret complexes does not depend on the optical activity of the substance. It is also particularly interesting to note that similar absorptions are exhibited not only be racemic and optically active alanyl peptides but also by the complex of the alanyl tripeptide whose amino acids do not all possess the same type of rotation (l-alanyl-d-alanyl-l-alanine). Not less important is the observation that the absorption by complexes of alanyl peptides is nearly identical with the absorption of the corresponding glycyl di- and tripeptides.

EXPERIMENTAL

Optically active forms of alanine were prepared by resolution of racemic carbobenzoxyalanine with the help of active papaine. The fermentative synthesis of the anilide proceeds only with the natural l-form of alanine in the form of the carbobenzoxy compound), the carbobenzoxy-d-alanine remaining in solution:

$$\underset{\underset{\underline{d,l}}{\mathrm{NH{-}OCOCH_2C_6H_5}}}{\mathrm{CH_3CHCOOH}} + \mathrm{H_2NC_6H_5} \longrightarrow \underset{\underset{\underline{l}}{\mathrm{NH{-}OCOCH_2C_6H_5}}}{\mathrm{CH_3CHCONHC_6H_5}} + \underset{\underset{\underline{d}}{\mathrm{NH{-}OCOCH_2C_6H_5}}}{\mathrm{CH_3CHCOOH}}$$

TABLE 3

Magnitudes of Optical Densities ε of Copper Biuret Complexes of Dipeptides (Concentration of Dipeptide M/150)

λ (in mμ)	Carbobenzoxy-alanyl-alanine	Alanylalanine (racemic)	Carbobenzoxy-l-alanyl-l-alanine	l-Alanyl-l-alanine	Carbobenzoxy-d-alanyl-l-alanine	d-Alanyl-l-alanine
480	0.0107	0.0310	0.0329	0.0489	0 0300	0.0185
500	0.0232	0.0402	0 0413	0.0491	0.0689	0 0421
520	0.0482	0.0799	0.0833	0.0696	0.0970	0.0855
540	0.0555	0.0870	0.0888	0.0930	0.1411	0.1121
560	0.0799	0.1098	0 1234	0.1049	0 1569	0.1270
580	0.1036	0 1160	0 1621	0.1162	0.1772	0 1324
600	0.1412	0.1504	0.2020	0.1506	0 1886	0 1822
620	0.1691	0.1600	0.2055	0.1608	0 2102	0 2050
640	0.1778	0.1705	0.2301	0 1704	0 2111	0 2101
650	0.1891	0 1770	0.2313	0.1760	0 2198	0.2359
660	0 1897	0.1790	0.2356	0.1790	0 1956	0.2442
670	0 1657	0.1810	0.2250	0.1818	0.1957	0 2485
680	0.1644	0.1851	0 2248	0.1886	0.1937	0 2377
700	0 1541	0.1720	0.2219	0.1732	0.1859	0 2025
730	0.1433	0.1350	0.1452	0 1304	0 1504	0 1933

Use was made of Bergman's method of resolution [4], which he proposed for the resolution of carbobenzoxy-d,l-leucine.

Preparation of the anilide of carbobenzoxy-l-alanine. 5 g carbobenzoxyalanine was dissolved in 25 ml 1 N NaOH, and addition was made of 45 ml 2 N sodium acetate, 75 ml citrate buffer, 50 ml papaine solution, 0.075 g freshly reduced cysteine hydrochloride, 5 g freshly distilled aniline and 1 ml glacial acetic acid. A transparent, faint yellow solution was obtained which was stood in a thermostat at 37°. After several hours flocs of the anilide appeared in the vessel, and after 2 days the amount was 2.3 g. The filtrate from the anilide was acidified with 5 N HCl until acid to Congo and extracted with ether. The ether solution was washed with water several times to remove the hydrochloric acid and dried overnight over sodium sulfate, after which the ether was distilled. Yield 3 g with m.p. 90-100°. Resolution evidently did not proceed to completion.

3 g of this substance was dissolved in 15 ml 1 N NaOH, and addition was made of 45 ml citrate buffer, 30 ml papaine solution, 0.045 g reduced cysteine and 3 g freshly distilled aniline. After standing for a day in the thermostat, another 0.5 g anilide came down. The precipitate was filtered and the solution again stood in the thermostat. After 24 hours, another 0.4 g anilide was obtained, making a total of 3.2 g of the anilide of the l-form from 5 g carbobenzoxyalanine. The theoretical yield was 3.3 g. The anilide was purified by recrystallization from alcohol. M.p. 159-160°.

Found %: N 9.23. $C_{17}H_{18}O_3N_2$. Calculated %: N 9.05. Specific rotation of a 6.25% solution in methyl acetoacetate $[\alpha]_D^{20} = \frac{-0.8 \cdot 100}{6.24 \cdot 1} = -12.8°$.

Hydrolysis of the anilide of carbobenzoxy-l-alanine. The literature does not contain any reference to the separation of the l-form by this method. For this purpose we carried out an acid hydrolysis:

$$\text{l-}CH_3CH(NH{-}COOCH_2C_6H_5)CONHC_6H_5 + HCl \longrightarrow \text{l-}CH_3CH(NH_3)COOH \cdot HCl + NH_2C_6H_5 + C_6H_5CH_2Cl + CO_2$$

5 g of the anilide of carbobenzoxy-l-alanine was refluxed for 6 hours on the boiling water bath with 50 ml concentrated HCl. Bubbles of gas came off at the start, indicating that hydrolysis of the carbobenzoxy group was proceeding. After 30 minutes the gas ceased to be evolved and the whole of the substance had dissolved in the

acid, the solution acquiring a brown color. The odor of benzyl chloride was detected. After hydrolysis, the solution was cooled and extracted twice with equal volumes of ether for removal of the benzyl chloride. The color of the solution then became lighter. The aqueous layer was evaporated in vacuum, the obtained substance was dissolved in the minimum amount of water and the solution was neutralized with 10% sodium carbonate solution. The aniline was then extracted with benzene and the solution again evaporated in vacuum to give 3.6 g of a yellow substance. The color disappeared after washing with alcohol. The substance was a mixture of sodium chloride and the sodium salt of l-alanine.

The amount of l-alanine salt was determined by formaldehyde titration which showed that the mixture was one-third by weight l-alanine, i.e. 1.2 g. Yield 85.6% of the theoretical.

Preparation of carbobenzoxy-l-alanine was carried out as for racemic alanine.

5 g of the mixture (l-alanine and NaCl), containing 1.5 g l-alanine, was taken. The reaction gave 3.1 g carbobenzoxy-l-alanine or 80.5% of the theoretical. M.p. 84°.

Specific rotation of a 2.5% solution in methyl alcohol: $[\alpha]_D^{20} = \frac{-0.26 \cdot 100}{0.8 \cdot 2.5} = -13°$.

Separation of carbobenzoxy-d-alanine. The mother liquor after removal of the anilide was acidified with 5 N HCl and extracted with ether. The ether layer was washed with water for removal of the HCl and dried with sodium sulfate; the ether was distilled in vacuum.

Yield 2.2 g with m.p. 80-84°. Recrystallization from hot water gave 1.8 g with m.p. 82-84°.

Carbobenzoxy-d-alanine has not previously been prepared. Bergman gives a m.p. of 84° for carbobenzoxy-l-alanine.

The rotation was determined on a 2.5% solution of the substance in methyl alcohol.

$$[\alpha]_D^{20} = \frac{+0.25 \cdot 100}{0.8 \cdot 2.5 \cdot 1} = +12.5°.$$

Carbobenzoxy-d-alanine does not crystallize so readily as racemic carbobenzoxyalanine. Crystallization requires a long period and intense cooling. Other properties are similar.

Synthesis of alanine dipeptides. Bergman's general method was used. Alanine dipeptides have not previously been obtained by this method. The principal difficulties in performing the syntheses were the following:

I. The acid chlorides of the carbobenzoxy-optically active forms of alanine have poor stability. The ethyl ether used as solvent must be well cooled; likewise the petroleum ether used for removing the phosphorus oxychloride.

II. Carbobenzoxyalanylalanine has fairly good solubility in water and organic solvents, and this hinders its purification from phosphoric acid. The latter is removed by dissolving the carbobenzoxy-dipeptide in methyl alcohol, adding 10% sodium carbonate solution until alkaline to litmus, evaporating to dryness in vacuum and working up the residue with absolute methyl alcohol. The sodium phosphate is filtered off. The solution of the carbobenzoxy-dipeptide salt in methyl alcohol is acidified with 20% HCl until acid to litmus and neutral to Congo red, and again evaporated to dryness; the carbobenzoxy-dipeptide was dissolved in methyl alcohol and filtered from the NaCl; the alcohol was distilled off and the carbobenzoxy-dipeptide isolated in the free state.

III. Reduction of carbobenzoxyalanyl dipeptides hardly proceeds in the conditions recommended by Bergman. Good results are obtained by reduction in an aqueous medium: 0.6-0.8 g carbobenzoxyalanine was put into 10 ml water and 1 ml glacial acetic acid. Prior to reduction this mixture was in the form of a suspension; with progressive reduction it gradually changed into a transparent solution. Reduction was effected by passing a stream of hydrogen in presence of palladium catalyst.

The following were prepared:

1) Racemic carbobenzoxyalanylalanine (an oil, very soluble in organic solvents and fairly soluble in water).

2) Carbobenzoxy-l-alanyl-l-alanine (an oil less soluble in water than the racemic carbobenzoxyalanyl-alanine).

3) Carbobenzoxy-d-alanyl-l-alanine (crystals melting at 120°; slow crystallization; poor solubility in water).

The alanine dipeptides crystallize with great difficulty. Tripeptides were synthesized starting from aqueous solutions of the dipeptides (2.8%) in which the ratio of total to amine nitrogen was determined by an analytical method.

The theoretical ratio of total N to amine N is 2.05. For racemic alanylalanine the value found was 2.2; for l-alanyl-l-alanine 2.08; for d-alanyl-l-alanine 2.3.

Alanine tripeptides were synthesized by Bergman's general method via the carbobenzoxy derivatives. Carbobenzoxy-tripeptides are obtained in the form of an oil with better solubility in water than the carbobenzoxy-dipeptides. Prior to reduction, the phosphoric acid was eliminated by the same method as was described above for carbobenzoxy-dipeptides. Reduction was performed in 9 ml water + 1 ml glacial acetic acid until the solution was completely cleared (1 hr). The catalyst was filtered off and the solution evaporated in vacuum; the last traces of water were distilled off with benzene and the tripeptide was crystallized. Alanine tripeptides are very soluble in water; they form a suspension in absolute methyl alcohol.

TABLE 4

Analysis of Tripeptides

Tripeptides	Nitrogen %		Total N: amine N
	Total	Amine	
Racemic alanylalanylalanine	18.21	5.5	3.27
l-Alanyl-l-alanyl-l-alanine	16.49	5.2	3.15
l-Alanyl-d-alanyl-l-alanine	16.51	5.1	3.23
Calculated for $C_9H_{17}O_4N_3$	18.18	6.07	3.23

Compounds prepared by this route were racemic alanylalanylalanine, m.p. 210° (with decomp.), l-alanyl-l-alanyl-l-alanine, m.p. 280° (with decomp.), and l-alanyl-d-alanyl-l-alanine m.p. 220° (with decomp.)

SUMMARY

1. Formation of the biuret complex of optically active peptides and proteins does not lead to racemization, thus indicating enolization of the peptide bonds during the biuret reaction and providing evidence of the presence of the enol form of the peptide bonds in the structure of the biuret complex of peptides and protein.

2. Formation of the biuret complex permits maintenance of the optical activity of proteins and peptides when exposed to the prolonged action of caustic alkali.

3. The optical activity of peptides does not exert a specific influence on the character of the absorption of biuret complexes in the visible region of the spectrum.

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Received April 2, 1951

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ISOQUINOLINE COMPOUNDS

IX. SYNTHESIS OF 1-[δ-(β-METHYL-α-PIPERIDONE)]-2-[1'-(3',4'-DIHYDRO-6',7'-DIMETHOXYISOQUINOLYL)]-ETHANE AND OF THE ETHYL ESTER OF N-HOMOVERATRYL-β-METHYL-α-PIPERIDONE-δ-PROPIONIC ACID

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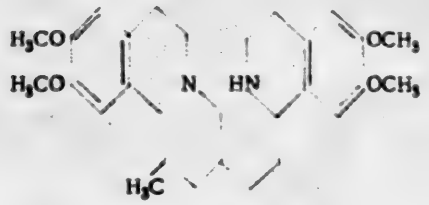
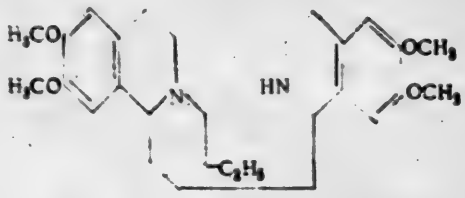
In connection with our studies of the synthesis of compound structurally similar to the alkaloid emetine, we prepared 1-[δ-(β-methyl-α piperidone)]-2-[1'-(3',4'-dihydro-6',7' dimethoxyisoquinolyl)]-ethane (I) and the ethyl ester of N-homoveratryl-β-methyl-α-piperidone-δ propionic acid (II). The synthesis of these compounds revealed the possibility of preparation of a compound with structure (III), possessing one of the formulas previously suggested for emetine.



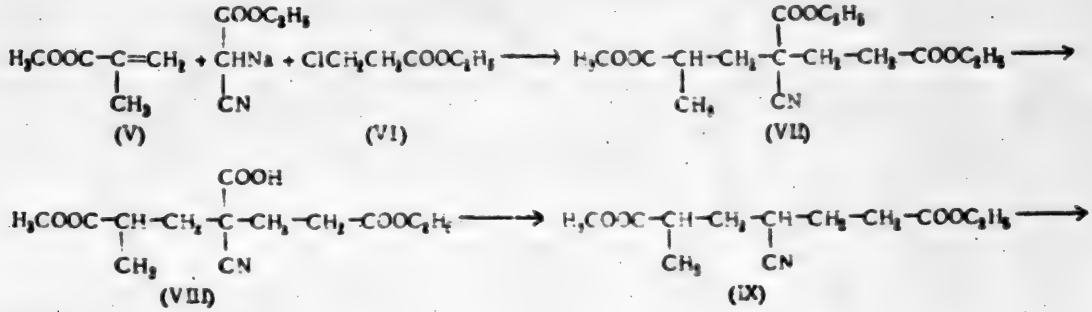
(III)



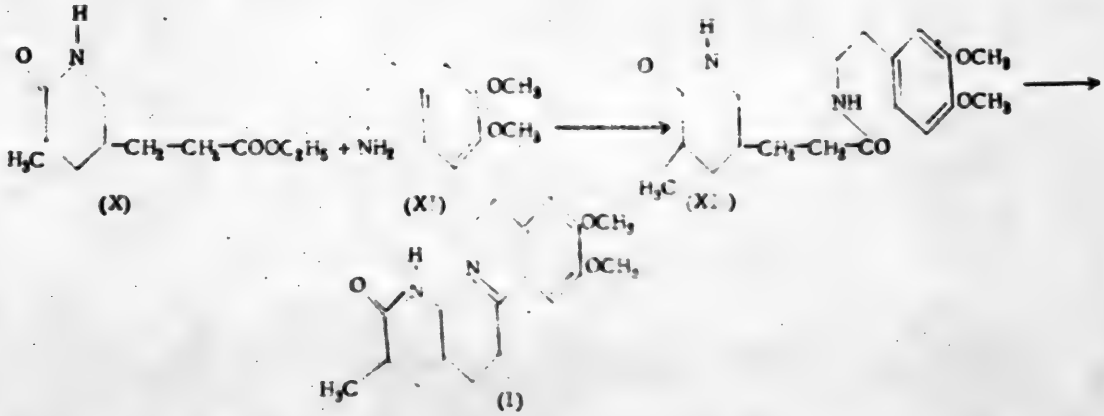
(IV)

We have previously shown [1], however, that the structure of emetine corresponds to formula (III) and not to formula (IV).

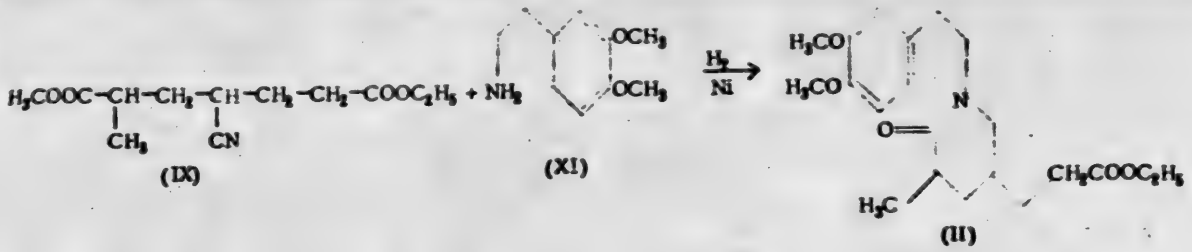
The synthesis described in this paper served as a model for the preparation of compounds required for synthesis of compounds containing the benzoquinolizine grouping. Compound (I) was synthesized according to the following scheme:



(V) (VI) (VII) (VIII) (IX)

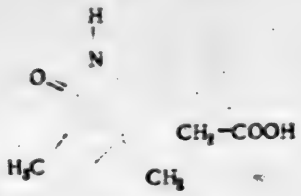


(X) (X') (X'') (I)



(IX) (XI) (II)

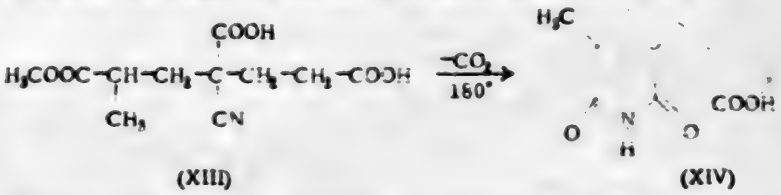
The methyl ester of methacrylic acid (V) condenses [2] with the ethyl ester of sodium cyanoacetate and the product of reaction, without isolation, is worked up with the ethyl ester of β-chloropropionic acid (VI). The resultant ester of α-methyl-γ-cyano-γ-carbethoxypimelic acid (VII) is converted by hydrolysis with one equivalent of alcoholic alkali into the monoacid (VIII), which is transformed by decarboxylation into the ester of α-methyl-γ-cyanopimelic acid (IX). Hydrogenation of the latter gives the derivative of α-piperidone (X), and this is hydrolyzed with one equivalent of alcoholic alkali to the acid (Xa).



(Xa)

Heating of the ester of β-methyl-α-piperidone-δ-propionic acid (X) with homoveratrylamine (XI) gives the corresponding amide (XII), which with phosphorus oxychloride is converted into a crystalline dihydroisoquinoline derivative [4]. If (X) is heated with β-phenylethylamine, a crystalline amide is obtained.

It is interesting to note that hydrolysis of the tricarboxylic ester (VII) with three equivalents of alcoholic alkali gives the tricarboxylic acid (XIII), but on decarboxylation this is converted not into α-methyl-γ-cyanopimelic acid but into the isomeric monobasic acid with the structure (XIV) [3]:



(XIII) (XIV)

Hydrolysis of the ester of α-methyl-γ-cyanopimelic acid (IX) in presence of homoveratrylamine (XI) gives the ethyl ester of N-homoveratryl-β-methyl-α-piperidone-δ-propionic acid [5] (II).

EXPERIMENTAL

1. Ester of α-methyl-γ-cyano-γ-carbethoxypimelic acid (VII). 11.5 g sodium is dissolved in 170 ml absolute alcohol and to the solution, after cooling, is added 56.5 g ethylcyanoacetate. To the resultant sodium derivative is added 50 g methylmethacrylate (b.p. 99-101°) and the mixture heated for an hour on the water bath. After cooling, slow addition is made to the solution of 70 g ethyl β-chloropropionate. Almost at once precipitation commences of sodium chloride and much heat is developed, necessitating periodic cooling with cold water. The solution is then heated on the water bath for two hours until disappearance of the alkaline reaction to litmus. The alcohol is distilled off in a low vacuum and water is added to the residue to dissolve the sodium chloride. The separated oil is extracted with benzene. After removal of the solvent, the residue is distilled. B.p. 197-199° (9 mm). Yield 126.5 g or 81% of the theoretical. n_D^{18} 1.4503.

3.220 mg substance: 6.800 mg CO_2, 2.140 mg H_2O. 5.320 mg substance: 0.216 ml N_2 (23°, 754 mm). Found %: C 57.59, H 7.44; N 4.64. $C_{15}H_{23}O_6N$. Calculated %: C 57.50; H 7.40; N 4.47.

2. Ester of α-methyl-γ-cyanopimelic acid (IX). An alcoholic solution of NaOH is prepared by dissolving 3.7 g sodium (1 g-atom) in 50 ml absolute alcohol and 2.9 g (1 mole) water. To the solution is added 50 g of the ester of α-methyl-γ-cyano-γ-carbethoxypimelic acid. Heat is developed and the solution acquires a viscous consistency. On the following day the alcohol is distilled off in vacuum, water is added and the residue of

alcohol distilled off in vacuum. The unsaponified tricarboxylic ester is extracted with benzene and the aqueous solution (cooled) is acidified with dilute hydrochloric acid. The separated oil is extracted with ether. After drying, the ether is removed and the residue of viscous oil (40 g) is heated for 40 minutes at 170-175° until carbon dioxide ceases to come off. After cooling, the mobile oil is dissolved in 50 ml benzene and the benzene solution washed 2-3 times with 5% NaOH solution for removal of acid impurities. After drying, the solvent is removed and the residue fractionated in vacuum. Yield 22 g (57.2% of the theoretical). B.p. 183-186° at 14 mm; n_D^{20} 1.4431. 5 g unsaponified ester is recovered unchanged.

3.345 mg substance: 7.360 mg CO_2; 2.350 mg H_2O. 5.620 mg substance: 0.298 ml N_2 (25°, 752 mm). Found %: C 60.01; H 7.86; N 6.01. $C_{12}H_{19}O_4N$. Calculated %: C 59.71; H 7.94; N 5.80.

3. Ethyl ester of β-methyl-α-piperidone-δ-propionic acid (X). Into an autoclave is charged 5 g pyrophoric nickel, 20 ml absolute alcohol and 19.2 g of the ester of α-methyl-γ-cyanopimelic acid. Hydrogenation is performed at 105-110° and 150-160 atm for an hour. The alcoholic solution is filtered fromcatalyst and the alcohol removed on the water bath. The residual thick oil is distilled in vacuum. B.p. 163-165° (3 mm). Yield 13.7 g (80.5% of theory). n_D^{20} 1.4830. Colorless, viscous oil.

3.5030 mg substance: 7.9530 mg CO_2; 2.6820 mg H_2O 4.4480 mg substance: 10.084 mg CO_2; 3.4070 mg H_2O. 5.910 mg substance: 0.345 ml N_2 (22°, 755 mm). Found %: C 61.92, 61.83, H 8.56, 8.57. N 6.71. $C_{11}H_{19}O_3N$ Calculated %: C 61.93; H 8.90. N 6.58.

When this compound is saponified with one equivalent of alcoholic KOH, β-methyl-α-piperidone-δ-propionic acid (Xa) is obtained. M.p. (from alcohol) 159-160°.

4.965 mg substance: 0.335 ml N_2 (21°, 750 mm) 4.945 mg substance: 0.324 ml N_2 (20°, 751 mm). Found %: N 7.73, 7.54. $C_9H_{15}O_3N$. Calculated %: N 7.57.

4. Homoveratrylamide of β-methyl-α-piperidone δ-propionic acid (XII). 3 g ethyl ester of β-methyl-α-piperidone-δ-propionic acid and 2.6 g homoveratrylamine are heated on an oil bath at 180-185° for 4 hours. After cooling, benzene is added and the mass dissolves when heated. While cooling, a colorless oil separates from the benzene solution. The benzene is decanted off and the product washed with a fresh portion of benzene. Clear, very viscous oil. Yield 4.5 g (79.2 % of the theoretical).

3.740 mg substance: 0.276 ml N_2 (24°, 737 mm). Found %: N 8.22. $C_{19}H_{28}O_4N_2$. Calculated %: N 8.04.

In a similar manner from β-phenylethylamine is obtained the phenylethylamide of β-methyl-α-piperidone-δ-propionic acid in crystalline form. M.p. (from alcohol) 162-163°.

4.051 mg substance. 0.346 ml N_2 (18°, 722 mm). Found %: N 9 52. $C_{17}H_{24}O_2N_2$. Calculated %: N 9.71.

5. 1-[δ-(β-Methyl-α-piperidone)] 2 [1'-(3',4'-dihydro 6',7' dimethoxyisoquinolyl)]-ethane (I). 1.8 g homoveratrylamide of β methyl-α-piperidone δ-propionic acid is dissolved by heating in 30 ml toluene and to the solution is added 4 ml phosphorus oxychloride. The mixture is heated at the gentle boil for an hour. After cooling, the weakly colored toluene solution is decanted from the precipitate. The latter is washed once with ether and dissolved in water. The aqueous solution is made alkaline with ammonia and the resultant oil is extracted with benzene. The benzene is distilled off in vacuum and the solid residue is transferred to a filter and washed with a little ether. Yield 1.05 g (61.5% of theory) M.p (from benzene) 165.5-166.5°.

5.805 mg substance: 0.438 ml N_2 (25°, 754 mm) Found %. N 8.57. $C_{19}H_{26}O_3N_2$. Calculated %: N 8 48

6. α-Methyl-γ-cyano-γ-carboxypimelic acid (XIII). An alcoholic solution of NaOH is prepared by dissolving 2.21 g (3 g-atoms) sodium in 50 ml absolute alcohol and 1 72 g (3 moles) water To the solution is added 10 g (1 mole) of the ester of α-methyl-γ-cyano-γ-carboxypimelic acid. Hydrolysis proceeds with considerable heat development and the viscosity increases due to separation of the sodium salt. After heating on the water bath for 4 hours, 50 ml water is added and the alcohol is distilled off in vacuum. The transparent aqueous solution is acidified with dilute hydrochloric acid and extracted with ether. After drying, the ether is driven off. The solid residue weighs 7 2 g (92 % of the theoretical). After recrystallization from ether, the m.p. is 169-170° (with decomp.).

4.250 mg substance: 0.224 ml N_2 (23°, 754 mm). Found %: N 6.03. $C_{10}H_{13}O_4N$ Calculated %: N 5.76.

Carbon dioxide was evolved when 7 g α-methyl-γ-cyano-γ-carboxypimelic acid was heated at 170-180°. After cooling, the substance is in the form of a light-brown vitreous mass. Yield 5.7 g.

0.2213 mg substance. Neutralization 9.50 ml 0.1146 N NaOH. Found: M 202. $C_9H_{13}O_4N$. Calculated: M 199.

7. Ethyl ester of N-homoveratryl- β-methyl-α-piperidone-δ-propionic acid (II). 10 g of the ester of α-methyl- γ-cyanopimelic acid was hydrogenated in presence of 20 ml absolute alcohol, 40 g homoveratrylamine and 5 g nickel catalyst at 105-110° and 150-160 atm. for 2 hours. A strong odor of ammonia was detected when the autoclave was opened. The catalyst was filtered off and the alcoholic solution evaporated in vacuum. The residue was dissolved in 100 ml benzene and the benzene solution washed with dilute hydrochloric acid to remove the excess of homoveratrylamine. The benzene was distilled off and the residue fractionated in vacuum. B.p. 225-229° at 1 mm. Yield 3.5 g (22.9% of the theoretical). The compound is a light-yellow, very viscous oil.

3.670 mg substance: 8.965 mg CO_2; 2.615 mg H_2O. 3.220 mg substance: 7.900 mg CO_2, 2.350 mg H_2O. 6.790 mg substance: 0.175 ml N_2 (22°, 745 mm). Found %: C 66.62, 66.90; H 8.16, 8.16; N 3.84. $C_{21}H_{31}O_5N$. Calculated %: C 66.80; H 8.28; N 3.71.

SUMMARY

1. Synthesis was effected through a series of stages of 1-[δ-(β-methyl-α piperidone)]-2-[1'-(3',4'-dihydro-6',7'-dimethoxyisoquinolyl)]-ethane and of the ethyl ester of N-homoveratryl-β-methyl-α piperidone-δ-propionic acid, which are the principal intermediate products in model syntheses of emetine.

2. A method is developed for the preparation of the starting materials for these compounds: the ester of α-methyl- γ cyanopimelic acid and the ester of β-methyl-α-piperidone-δ-propionic acid.

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Received March 31, 1951

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• See Consultants Bureau Translation, p. 1611.

ISOQUINOLINE COMPOUNDS

X. SYNTHESIS OF 1-β-[(N-DECYL)-3'-PIPERIDYL]-ETHYL-6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISOQUINOLINE

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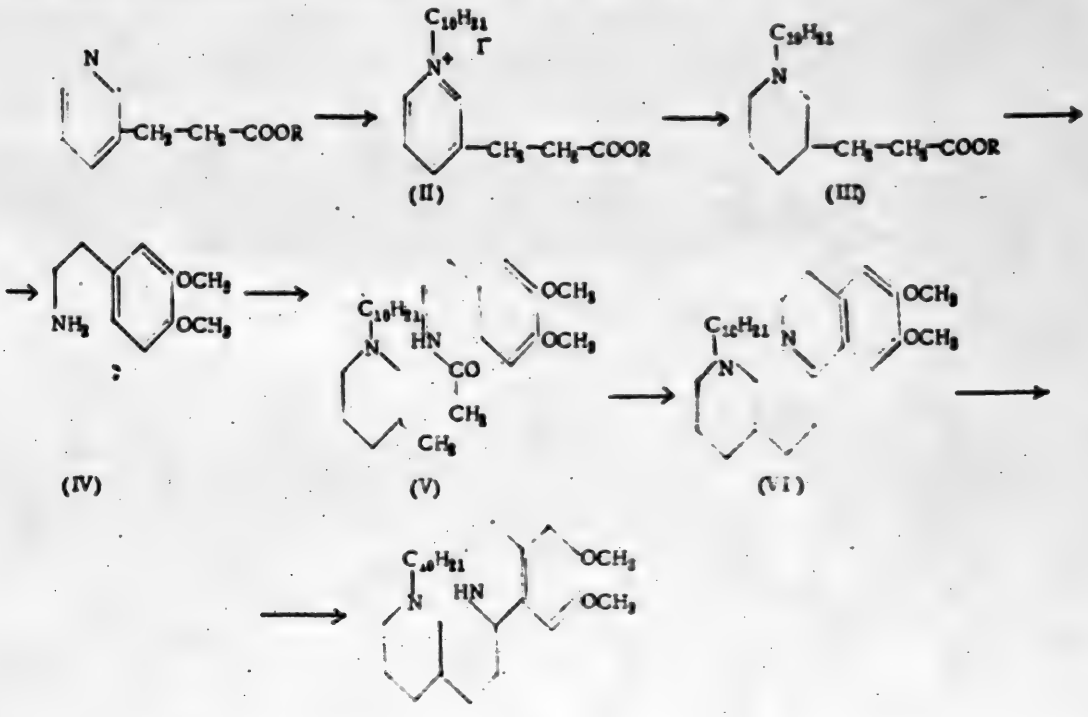
In view of the valuable physiological action of the alkaloid emetine, it is undoubtedly of interest to prepare simpler compounds containing the fundamentals of its structure. In this manner we may elucidate the influence of the individual structural fragments of the emetine molecule by observing their physiological effects. We effected the synthesis of 1-β-[(N-decyl)-3'-piperidyl]-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I), a compound whose structure differs from one of the formulas proposed for the natural alkaloid mainly in that the benzoquinolizine ring is substituted by a piperidine ring with an aliphatic radical attached to nitrogen and containing the same number of carbon atoms as in the absent part of the benzoquinolizine ring. The synthesis of compound (I) proceeded according to the following scheme:



The quaternary salt (II), prepared by condensation of the ester of β-(3-pyridyl)-propionic acid with decyl iodide, is reduced in presence of platinum oxide to the ester of β-[(N-decyl)-3-piperidyl]-propionic acid (III). This ester is heated with excess of homoveratrylamine (IV) at 180-185° to give β-(3',4'-dimethoxyphenyl)-ethylamide-β-[(N-decyl)-3-piperidyl]-propionic acid (V). Under the action of phosphorus oxychloride the amide (V) undergoes cyclization to the isoquinoline derivative (VI). The base (VI) is reduced by zinc and sulfuric acid to 1-β-[(N-decyl)-3'-piperidyl]-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I). Treatment with an ethereal solution of hydrogen chloride converts it into the hydrochloride.

* Deceased.

EXPERIMENTAL

Decoiodide of β-(3-pyridyl)-propionic acid ethyl ester (II). 4.4 g (1 mole) of the ethyl ester of β-(3-pyridyl)-propionic acid and 7 g (1.1 moles) decyl iodide are heated at 100-105° and 15-20 mm for 2 hours. The reaction mass—a yellow oil—is washed several times with absolute ether. Yield of quaternary salt 10.2 g (92.5 % of the theoretical). Readily soluble in alcohol and benzene, insoluble in ether and cold water.

8.610 mg substance: 0.227 ml N_2 (18.5°, 747 mm). 8.950 mg substance: 0.249 ml N_2 (19°, 748 mm). Found %: N 3.00, 3.14. $C_{28}H_{54}O_2NI$. Calculated %: N 3.13.

Ethyl ester of β-[(N-decyl)-3-piperidyl]-propionic acid (III). A solution of 10 g decoiodide of β-(3-pyridyl)-propionic acid ethyl ester in 30 mg absolute alcohol and 1 ml glacial acetic acid is hydrogenated at 0.8 atm pressure over 0.3 g platinum oxide. Yield 9.2 g (90.8 % of the theoretical). M.p. 89-90°. The hydroiodide is a colorless, crystalline substance, soluble in alcohol, benzene and chloroform, insoluble in ether and water.

7.900 mg substance: 0.217 ml N_2 (21.5°, 751.5 mm). 7.355 mg substance: 0.202 ml N_2 (1.5°, 751 mm). Found %: N 3.11, 3.10. $C_{28}H_{46}O_2NI$. Calculated %: N 3.09.

A solution of 9 g of the hydroiodide in a little dry chloroform is treated with chloroform saturated with ammonia while cooling. Partial distillation of the chloroform in vacuum and addition of absolute ether led to complete precipitation of the ammonium iodide. Yield 5.76 g (89.2% of theory). The ester is a colorless liquid with b.p. 194-195° at 5 mm, soluble in alcohol, chloroform and benzene, insoluble in water.

n_D^{20} 1.4639; d_{20}^{20} 0.9131; MR_D 98.29, calculated 97.95. 3.460 mg substance: 9.340 mg CO_2; 3.710 mg H_2O. 3.225 mg substance: 8.715 mg CO_2; 3.505 mg H_2O. 8.135 mg substance: 0.322 ml N_2 (20° 745 mm). 6.465 mg substance: 0.252 ml N_2 (21°, 743 mm). Found %: C 73.61, 73.69; H 12.0, 12.15; N 4.41, 4.34. $C_{28}H_{39}O_2N$. Calculated %: C 73.77; H 12.08; N 4.30.

β-(3',4'-Dimethoxyphenyl)-ethylamide of β-[(N-decyl)-3-piperidyl]-propionic acid (V). 2 g (1 mole) ethyl ester of β-[(N-decyl)-3-piperidyl]-propionic acid, 2.2 g (2 moles) β-(3,4-dimethoxyphenyl)-ethylamine and a few drops of pyridine are heated at 180-185° for 2 hours. With cooling, the reaction mass is triturated several times with dry ligroin. Yield of amide 2 g (70%). After recrystallization from benzene, the m.p. is 89-90°. Colorless crystals, soluble in alcohol, benzene, hot gasoline and water; insoluble in ligroin and ether.

2.930 mg substance: 7.870 mg CO_2; 2.755 mg H_2O. 4.720 mg substance: 0.255 ml N_2 (23°, 746 mm). 4.535 mg substance: 0.245 ml N_2 (23°, 746 mm). Found %: C 73.25; H 10.5; N 5.98, 6.02. $C_{28}H_{48}O_3N_2$. Calculated %: C 72.98; H 10.51; N 6.08.

1-β-[(N-decyl)-3'-piperidyl]-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VI). 2 g β-(3',4'-dimethoxyphenyl)-ethylamide of β-[(N-decyl)-3-piperidyl]-propionic acid, 20 ml absolute toluene and 14 ml phosphorus oxychloride are heated at 80° for 2 hours. The reaction mass is worked up and 0.8 g viscous, yellow oil is isolated from the benzene extract.

The picrate is prepared by reacting a benzene solution of the base with an ethereal solution of picric acid. M.p. (from alcohol) 162-163°. Yellow crystals, readily soluble in chloroform, poorly soluble in alcohol and cold water, insoluble in ether.

2.255 mg substance: 0.254 ml N_2 (23°, 742 mm). 2.225 mg substance: 0.247 ml N_2 (23°, 741 mm). Found %: N 12.41, 12.33. $C_{28}H_{48}O_3N_2 \cdot 2C_6H_3O_7N_3$. Calculated %: N 12.44.

1-β-[N-Decyl)-3'-piperidyl]-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I). 1 g 1-β-[N-decyl)-3'-piperidyl]-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline was reduced in a medium of 30 ml water, 5 g zinc dust and 3 ml sulfuric acid (sp.gr. 1.84). Yield of reduced base 0.7 g (70% of the theoretical).

Treatment of a benzene solution of the base with an ethereal solution of HCl gave an oil which crystallized after rubbing. The hydrochloride is a hygroscopic substance, readily soluble in alcohol, chloroform and water, insoluble in ether. M.p. 155-162°, deliquesces at 100-102°.

2.995 mg substance: 7.095 mg CO_2; 2.55 mg H_2O. 7.825 mg substance: 0.385 ml N_2 (22°, 742 mm). 4.240 mg substance: 0.216 ml N_2 (22°, 742 mm). Found %: C 64.61; H 9.53; N 5.46, 5.64. $C_{28}H_{48}O_2N_2 \cdot 2HCl$. Calculated %: C 64.94; H 9.35; N 5.41.

SUMMARY

1. The simplest analog of the alkaloid emetine was synthesized: 1-β-[(N-decyl)-3'-piperidyl]-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.

2. Methods were developed for the preparation of: the decoiodide of β-(3-pyridyl)-propionic acid ethyl ester: the ethyl ester of β-[(N-decyl)-3-piperidyl]-propionic acid: β-(3',4'-dimethoxyphenyl)-ethylamide of β-[N-decyl)-3-piperidyl]-propionic acid: and 1-β-[(N-decyl)-3'-piperidyl]-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline.

Received March 31, 1951

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